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(54) **PEPTIDIC CHIMERIC ANTIGEN RECEPTOR T CELL SWITCHES AND USES THEREOF**

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A61K 39/00	(2006.01)

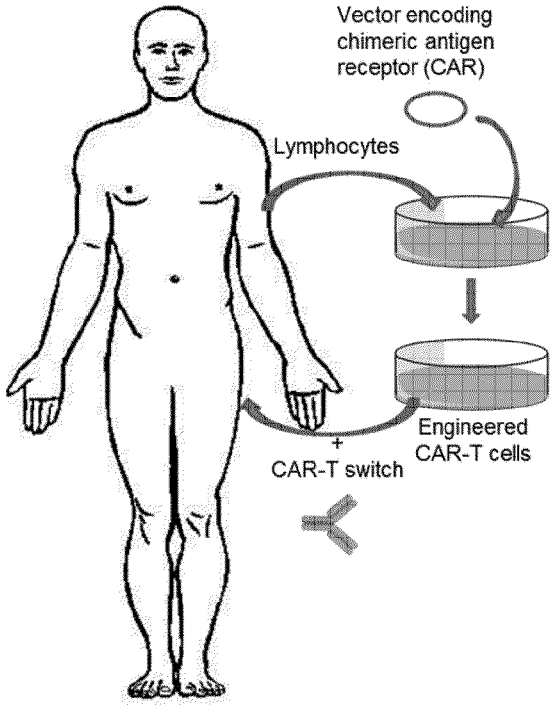
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(57) **ABSTRACT**

Disclosed herein are chimeric antigen receptor effector cells (CAR-ECs) and CAR-EC switches. The switchable CAR-ECs are generally T cells. The one or more chimeric antigen receptors may recognize a peptidic antigen on the CAR-EC switch. The CAR-ECs and switches may be used for the treatment of a condition in a subject in need thereof.

Specification includes a Sequence Listing.



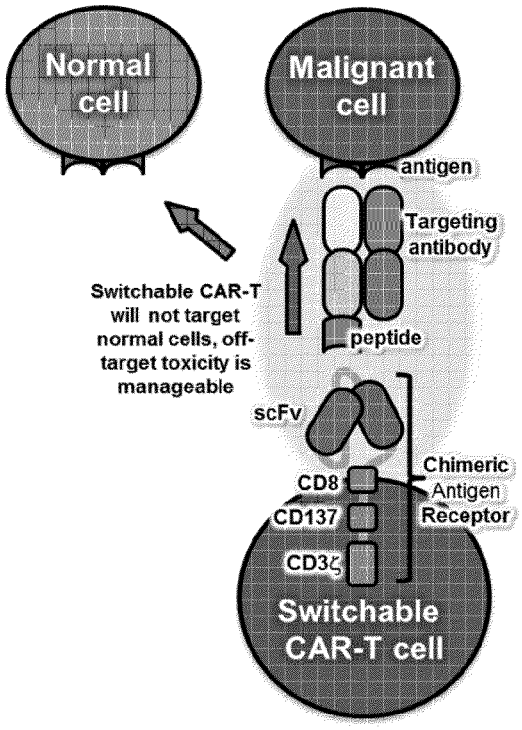


FIG. 1A

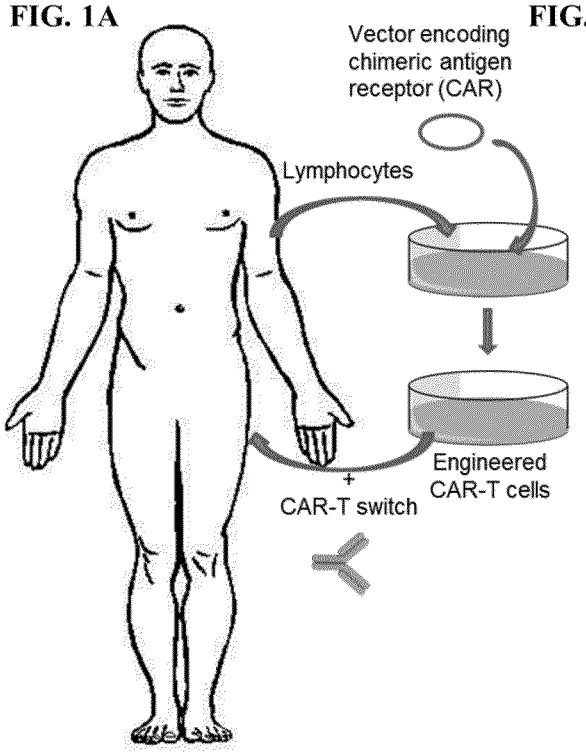


FIG. 1B

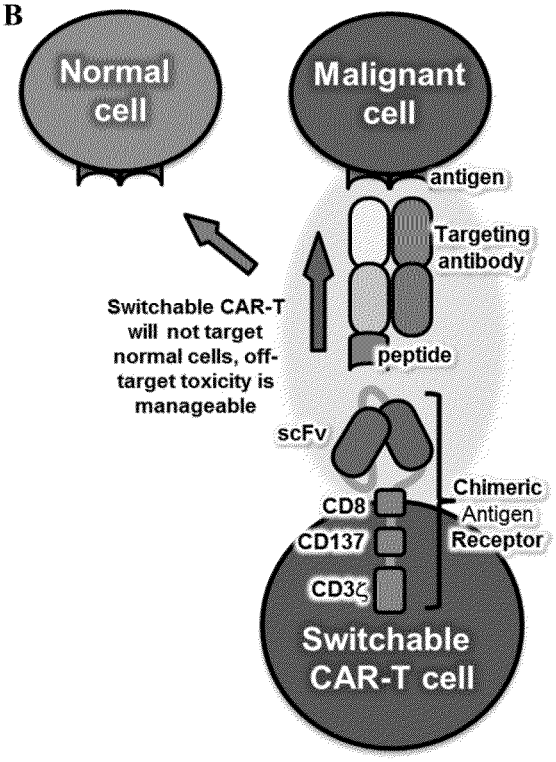


FIG. 2

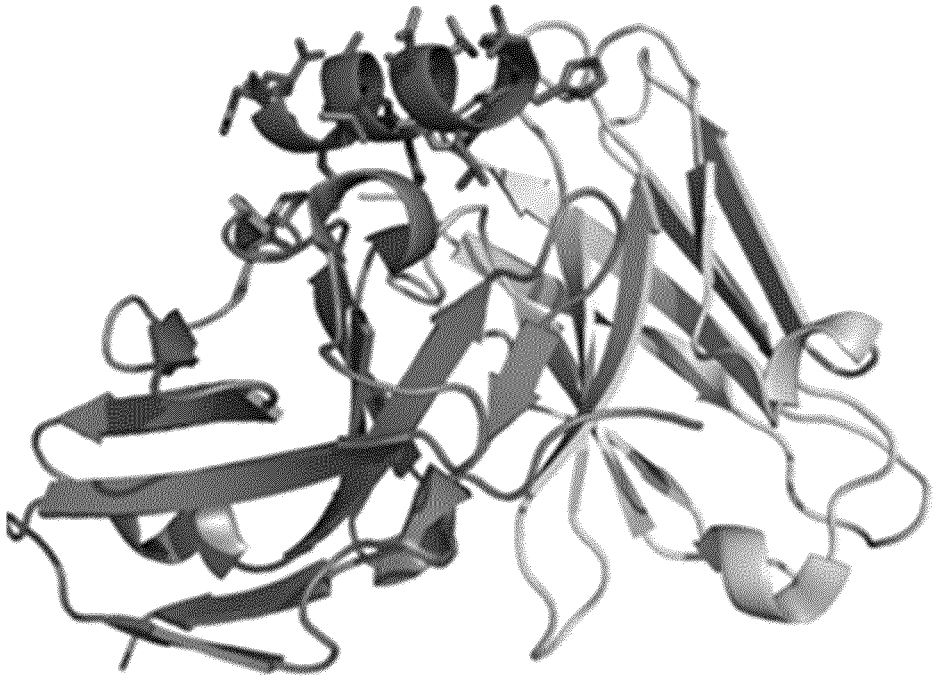


FIG. 3

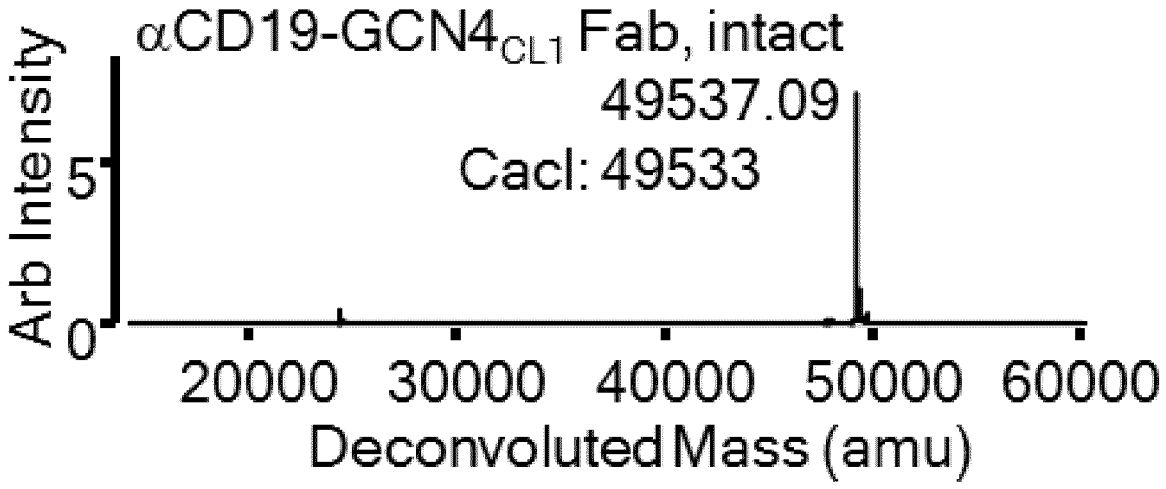

αCD19-GCN4CL1 Fab, intact
49537.09
Cacl: 49533
Arb Intensity
5
0
20000
30000
40000
50000
60000
Deconvoluted Mass (amu)

FIG. 4

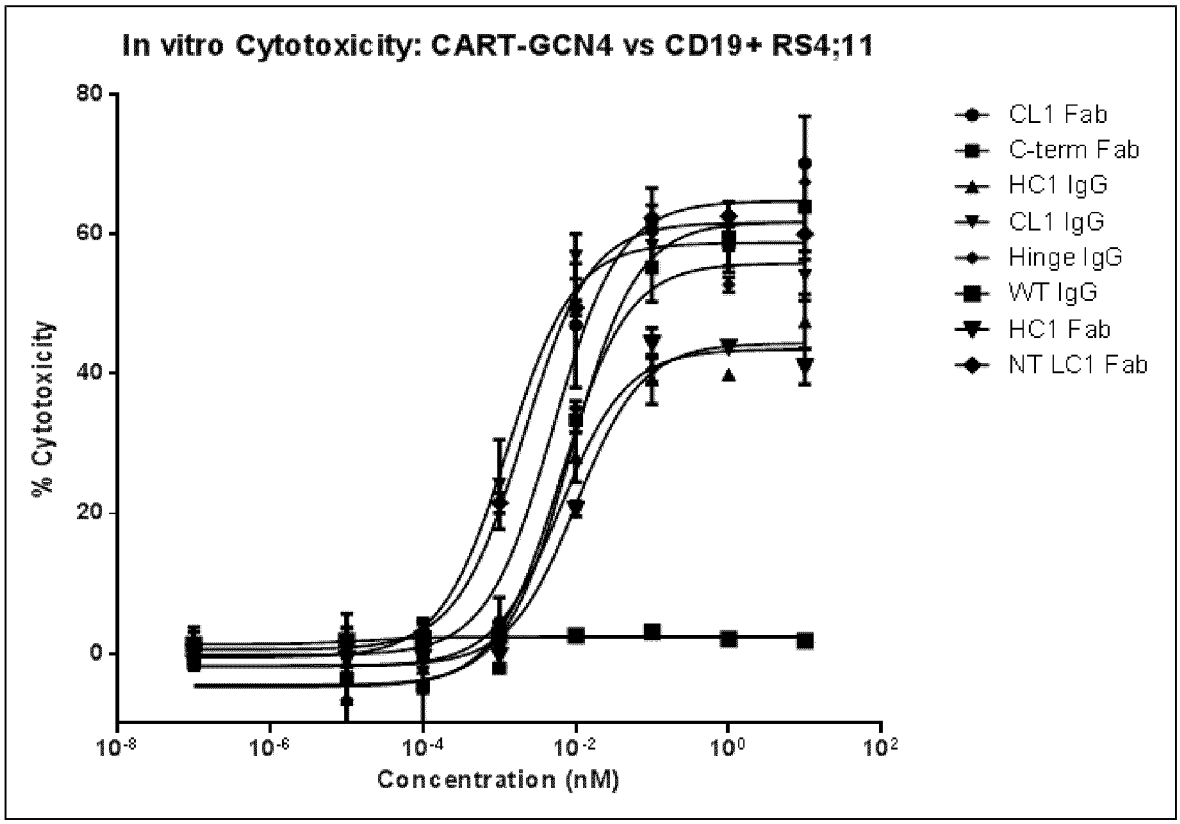

In vitro Cytotoxicity: CART-GCN4 vs CD19+ RS4;11
% Cytotoxicity
80
60
40
20
0
10-8
10-6
10-4
10-2
100
102
Concentration (nM)
CL1 Fab
C-term Fab
HC1 IgG
CL1 IgG
Hinge IgG
WT IgG
HC1 Fab
NT LC1 Fab

FIG. 5A

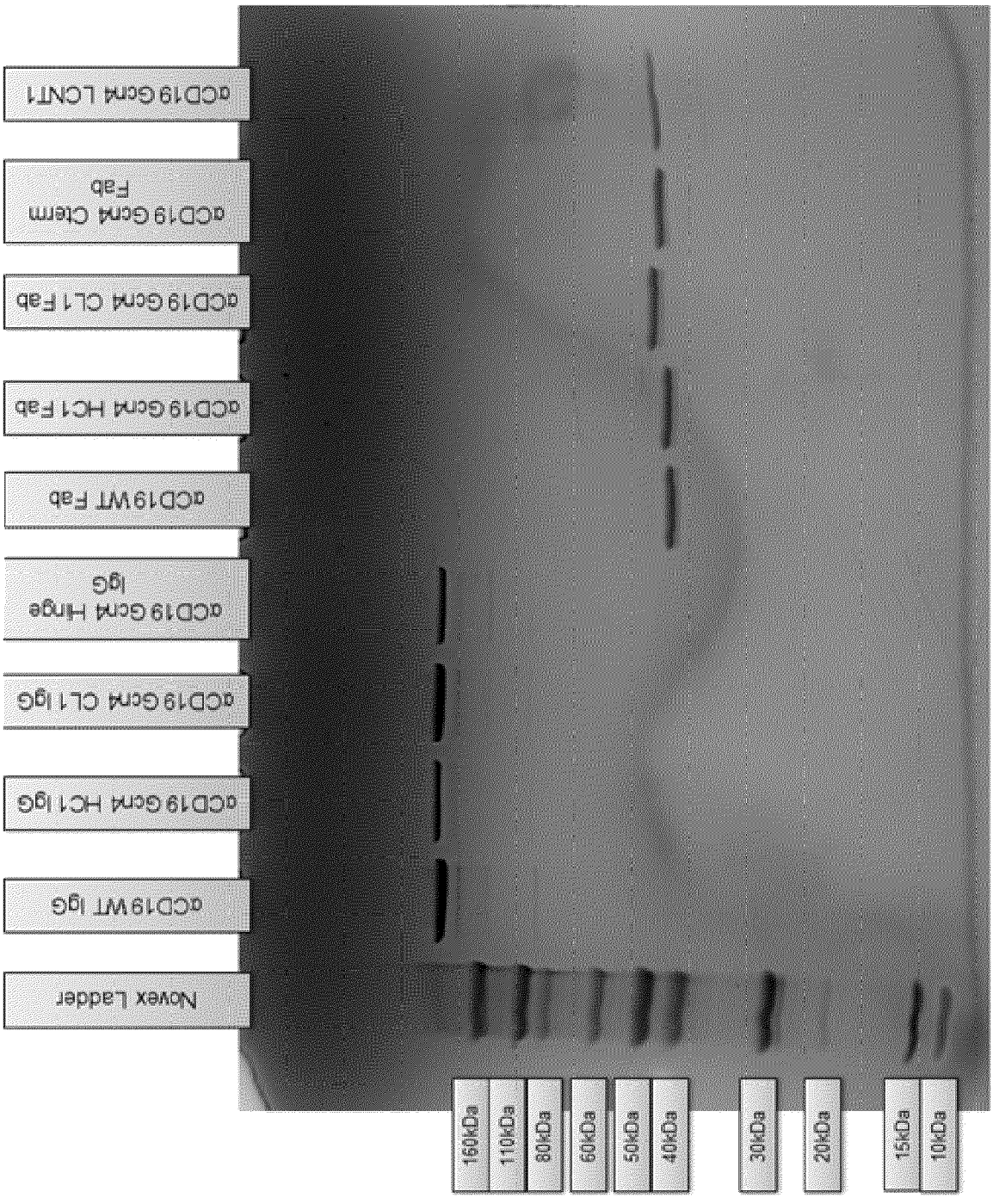

Novex Ladder
αCD19 WT IgG
αCD19 Gcn4 HC1 IgG
αCD19 Gcn4 CL1 IgG
αCD19 Gcn4 Hinge IgG
αCD19 WT Fab
αCD19 Gcn4 HC1 Fab
αCD19 Gcn4 CL1 Fab
αCD19 Gcn4 Cterm Fab
αCD19 Gcn4 LCNT1
160kDa
110kDa
80kDa
60kDa
50kDa
40kDa
30kDa
20kDa
15kDa
10kDa

FIG. 5B

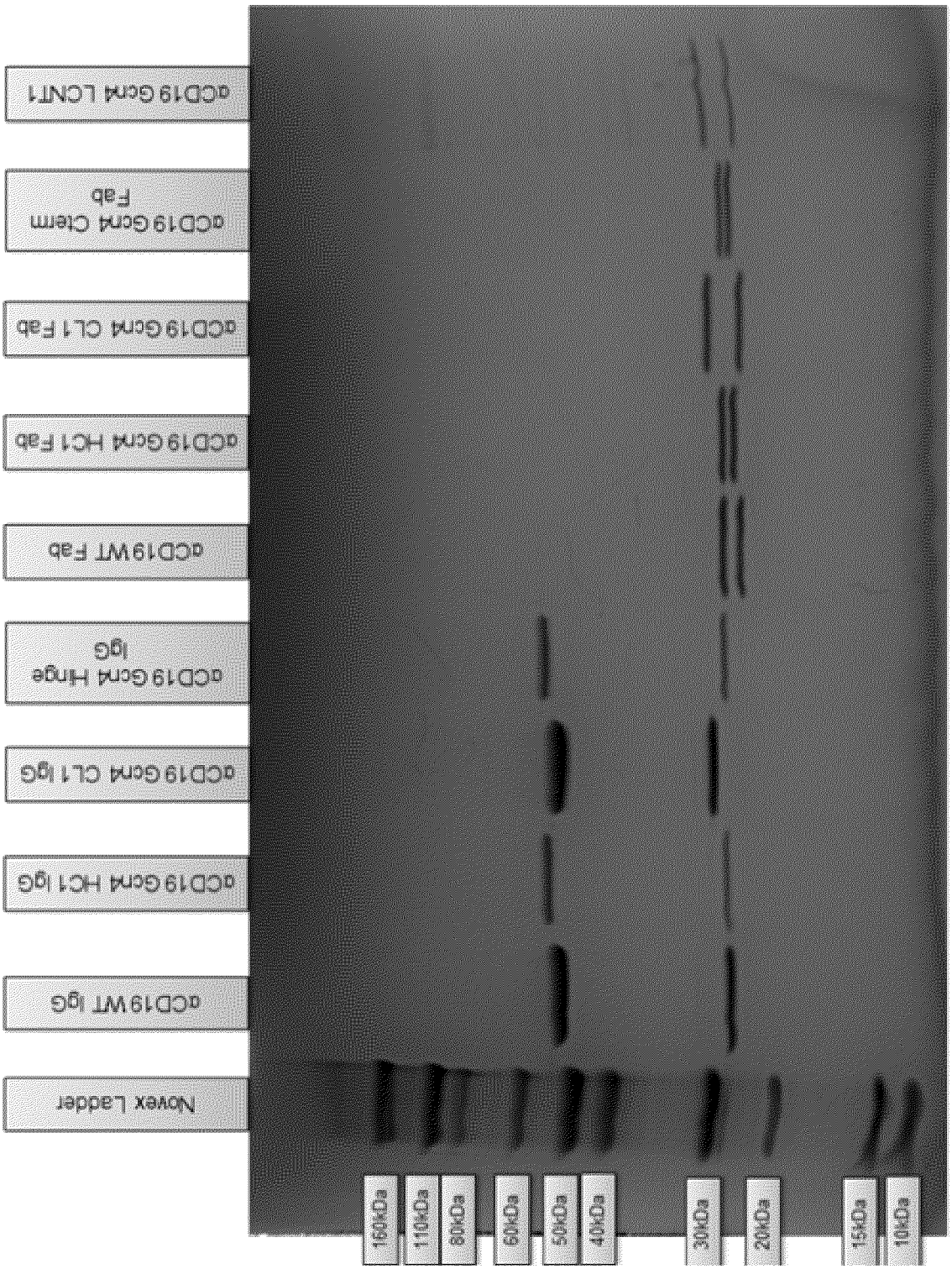

Novex Ladder
αCD19 WT IgG
αCD19 Gcn4 HC1 IgG
αCD19 Gcn4 CL1 IgG
αCD19 Gcn4 Hinge IgG
αCD19 WT Fab
αCD19 Gcn4 HC1 Fab
αCD19 Gcn4 CL1 Fab
αCD19 Gcn4 Cterm Fab
αCD19 Gcn4 LCNT1
160kDa
110kDa
80kDa
60kDa
50kDa
40kDa
30kDa
20kDa
15kDa
10kDa

FIG. 6

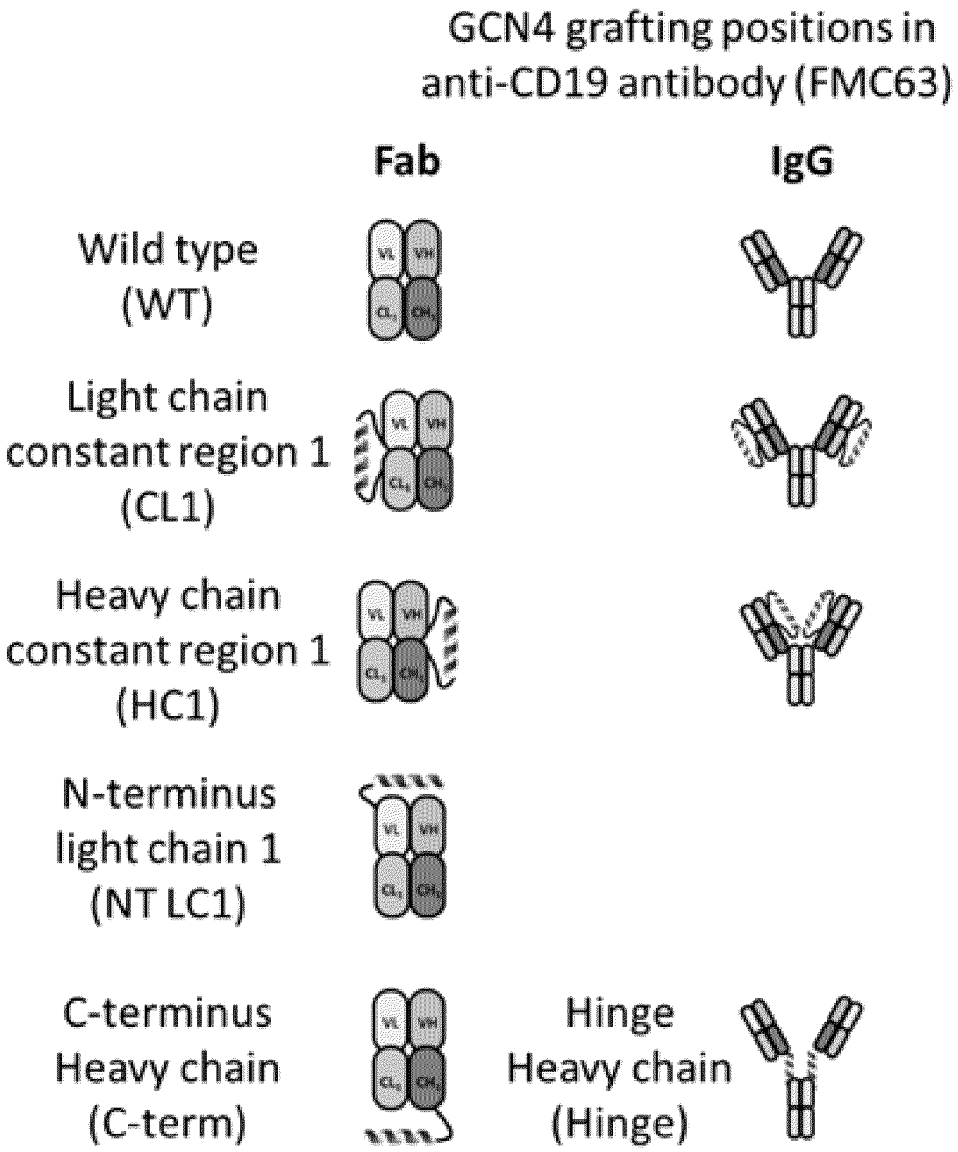

GCN4 grafting positions in
anti-CD19 antibody (FMC63)
Fab
IgG
Wild type
(WT)
Light chain
constant region 1
(CL1)
Heavy chain
constant region 1
(HC1)
N-terminus
light chain 1
(NT LC1)
C-terminus
Heavy chain
(C-term)
Hinge
Heavy chain
(Hinge)

FIG. 7A

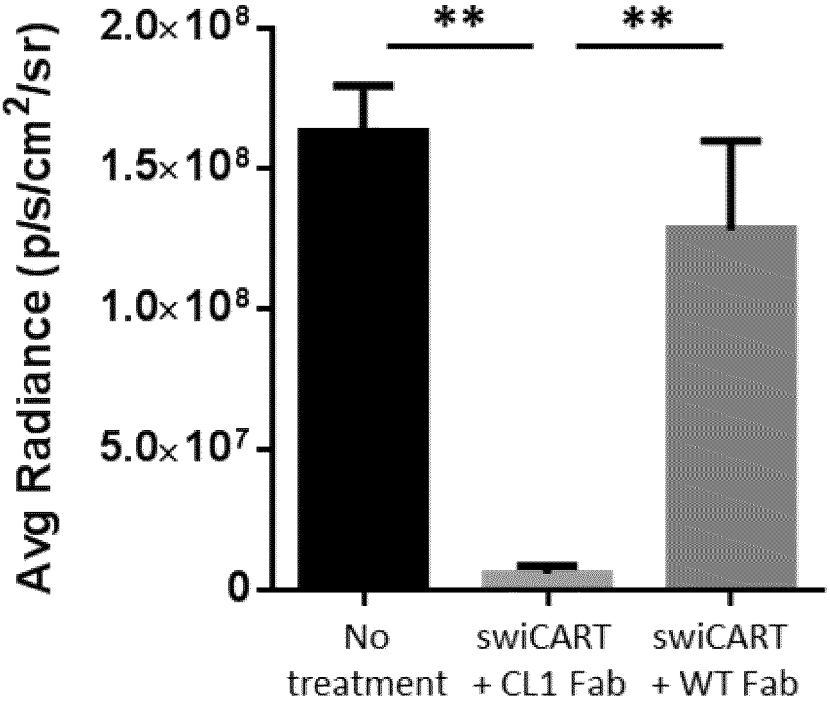
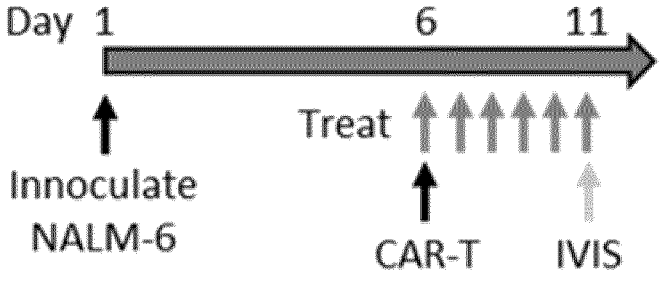

Avg Radiance (p/s/cm²/sr)
2.0×10⁸
1.5×10⁸
1.0×10⁸
5.0×10⁷
0
**
**
No treatment
swiCART + CL1 Fab
swiCART + WT Fab

FIG. 7B


Day 1
6
11
Treat
Innoculate NALM-6
CAR-T
IVIS

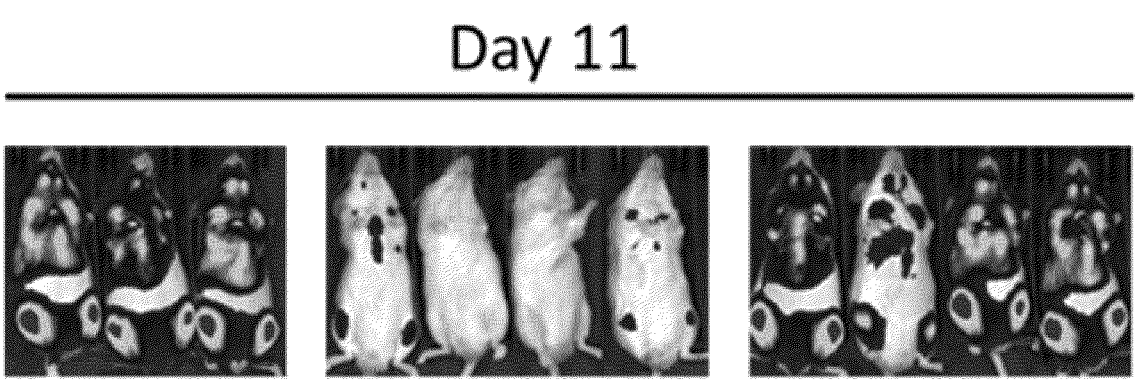
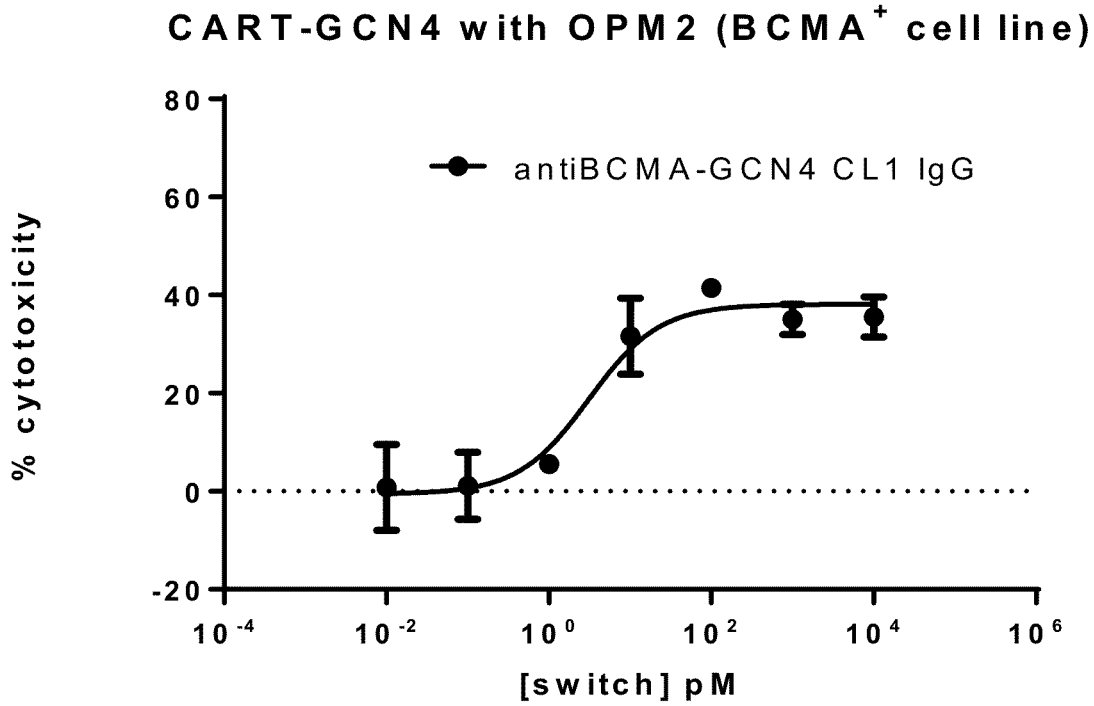

Day 11

FIG. 8



	antiBCMA-GCN4 CL1 IgG
IC50	3.093

PEPTIDIC CHIMERIC ANTIGEN RECEPTOR T CELL SWITCHES AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation of U.S. Application No. 17/713,489 (filed on Apr. 5, 2022; now pending), which is a continuation of U.S. Application No. 16/532,860 (filed on Aug. 6, 2019; now abandoned), which is a continuation of U.S. Application No. 15/448,477 (filed on Mar. 2, 2017; now U.S. Pat. No. 10,391,155), which is a continuation of U.S. Application No. 14/688,894 (filed on Apr. 16, 2015; now U.S. Pat. No. 9,624,276), which is a continuation of International Application No. PCT/US14/60684 (filed on Oct. 15, 2014; now expired), which claims the benefit of priority to U.S. Provisional Application No. 61/891,347 (filed on Oct. 15, 2013; now expired), U.S. Provisional Application No. 61/895,704 (filed on Oct. 25, 2013; now expired), U.S. Provisional Application No. 62/009,054 (filed on Jun. 6, 2014; now expired), U.S. Provisional Application No. 62/030,526 (filed on Jul. 29, 2014; now expired); and U.S. Provisional Application No. 62/030,514 (filed on Jul. 29, 2014; now expired). The disclosures of these priority applications are herein incorporated by reference in their entirety and for all purposes.

STATEMENT REGARDING SEQUENCE LISTING

[0002] The Sequence Listing associated with this application is provided in .xml format in lieu of a paper copy, and is hereby incorporated by reference into the specification. The .xml file is about 88 KB, created on Nov. 8, 2022, and is being submitted electronically via EFS-Web.

BACKGROUND OF THE INVENTION

[0003] Immunotherapies are becoming attractive alternatives to chemotherapies, including immunotherapies that use adoptive transfer of genetically modified T cells to "reteach" the immune system to recognize and eliminate malignant tumor cells. Genetically modified T cells express chimeric antigen receptors, which generally consist of a signaling endodomain, a CD3-zeta transmembrane domain and an extracellular single-chain variable fragment (scFv) derived from a monoclonal antibody which gives the receptor specificity for a tumor-associated antigen on a target malignant cell. Upon binding the tumor-associated antigen via the chimeric antigen receptor, the chimeric antigen receptor expressing T cell (CAR T-cell) mounts an immune response that is cytotoxic to the malignant cell. Such therapies can circumvent chemotherapy resistance and have been shown to be active against relapsed/refractory disease, resulting in sustained remissions for some chronic lymphocytic leukemia (CLL) and acute lymphoblastic leukemia (ALL) patients. However, these therapies require further investigation and optimization, as they caused undesirable effects such as toxic lymphophenia, chronic hypogammaglobulinemia for hematological targets, fatal off-target cytolysis for solid tumor targets, persistent B cell aplasia with the use of anti-CD19 antibody expressing CAR T-cells, and, in some cases, death.

[0004] Introduction of a switch, which controls the activity of the CAR T-cell, would allow CAR T-cell activity and associated immune responses to be turned off after neoplastic cells are eliminated and would allow B cells to reproliferate. Recent preclinical studies have demonstrated that CAR T-cell systems can be controlled through an antibody-based switch, wherein the antibody binds the target cell (e.g. cancer cell), blocking the CAR T-cell from binding the target cell and "switching off" CAR-T activity. While these systems conceptually allow for switchable targeting of tumors using CAR T-cells, they may suffer from a series of limitations. Non-specific labeling of antibodies using cysteines or lysines produces heterogeneous products which includes variants that may be non-functional, have unpredictable pharmacokinetics and/or immunogenicity, and that may be difficult to optimize.

SUMMARY OF THE INVENTION

[0005] Disclosed herein are chimeric antigen receptor-effector cell switches comprising: a peptidic antigen that binds a chimeric antigen receptor on an effector cell; and a targeting moiety that binds a cell surface molecule on a target cell. The peptidic antigen may be based on or derived from a naturally occurring peptide. The peptidic antigen may be based on or derived from a non-human peptide. The peptidic antigen may be based on or derived from a eukaryotic peptide. The peptidic antigen may be based on or derived from a peptide, wherein the peptide is expressed by a yeast. The peptidic antigen may be based on or derived from a yeast transcription factor GCN4. The peptidic antigen may comprise a non-naturally occurring peptide. The peptidic antigen may comprise a synthetic peptide tag. The peptidic antigen may be based on or derived from a sequence selected from SEQ ID NOs: 2-7. The peptidic antigen may comprise a sequence that is at least about 50% homologous to a peptide sequence selected from SEQ ID NOs: 2-7. The targeting moiety may comprise a targeting peptide. The targeting moiety may comprise a targeting antibody or antibody fragment. The targeting antibody or antibody fragment may be selected from the group consisting of: an immunoglobulin, an Fc null immunoglobulin, and a Fab, and fragments thereof. The targeting moiety may be selected from the group consisting of: an anti-EGFR antibody, an anti-Her2 antibody, anti-EGFRvIII antibody, an anti-CD33 antibody, an anti-CLL-1 antibody, an anti-CEA antibody, an anti-CD19 antibody, an anti-CD22 antibody, an anti-BCMA antibody, and an anti-CS1 antibody, and fragments thereof. The targeting antibody or antibody fragment may comprise a light chain and a heavy chain pair, wherein the light chain and heavy chain are encoded by nucleic acid sequences based on or derived from nucleic acid sequence pairs selected from the group consisting of: SEQ ID NOs: 8 and 9; SEQ ID NOs: 8 and 10; SEQ ID NOs: 11 and 12; SEQ ID NOs. 13 and 14; SEQ ID NOs: 15 and 16; SEQ ID NOs: 17 and 18; and SEQ ID NOs: 19 and 20. The targeting antibody or antibody fragment may comprise a light chain and a heavy chain pair, wherein the light chain and heavy chain are encoded by amino acid sequences based on or derived from amino acid sequence pairs selected from the group consisting of: SEQ ID NOs: 21 and 22; SEQ ID NOs: 23 and 24; SEQ ID NOs. 25 and 26; SEQ ID NOs: 27 and 28; and SEQ ID NOs: 27 and 29. The chimeric antigen receptor-effector cell switch may comprise a light chain and a heavy chain pair, wherein the light chain and heavy chain are encoded by amino acid sequences based

on or derived from amino acid sequence pairs selected from the group consisting of: SEQ ID NOs: 30 and 29; SEQ ID NOs: 36 and 29; SEQ ID NOs: 31 and 28; SEQ ID NOs: 27 and 32; SEQ ID NOs: 27 and 33; SEQ ID NOs: 27 and 34; and SEQ ID NOs: 27 and 35. The peptidic antigen may be fused to a terminus of the targeting antibody or antibody fragment. The peptidic antigen may be fused to a region of the targeting antibody or antibody fragment selected from the group consisting of: an N terminus of a light chain, a C terminus of a light chain, an N terminus of a heavy chain, a C terminus of a Fab heavy chain and a C terminus of a constant region heavy chain. The peptidic antigen may be grafted into the targeting moiety. The targeting moiety may comprise a targeting antibody or antibody fragment. The peptidic antigen may be grafted into a region of the targeting antibody or antibody fragment selected from a CH_1 domain, a CH_2 domain, a CH_3 domain, a CL domain, a VH domain, a VL domain and a hinge region. The peptidic antigen may be grafted between two regions of the targeting antibody or antibody fragment selected from a CH_1 domain, a CH_2 domain, a CH_3 domain, a CL domain, a VH domain, a VL domain, a heavy chain, a light chain and a hinge region, wherein the two regions are adjacent. The peptidic antigen may be grafted into a loop of the targeting antibody or antibody fragment. The peptidic antigen may be grafted into a loop of a constant domain of the targeting antibody or antibody fragment. The peptidic antigen may be grafted between the hinge region and a heavy chain constant domain of the targeting antibody or antibody fragment. The peptidic antigen may replace one or more amino acids of the targeting antibody or antibody fragment. The peptidic antigen may be grafted into the targeting antibody or antibody fragment without replacing an amino acid. The chimeric antigen receptor-effector cell may further comprise a linker that links the peptidic antigen and the targeting moiety. The linker may be a peptide that links the peptidic antigen and the targeting moiety, wherein the targeting moiety comprises a targeting polypeptide. The linker may comprise about 1 to about 20 amino acids. The linker may comprise a sequence based on or derived from a sequence selected from SEQ ID NOs: 38-42. The peptidic antigen may comprise a yeast transcription factor GCN4 or homolog thereof and the targeting moiety is selected from the group consisting of: an anti-Her2 antibody, an anti-BCMA antibody, an anti-CD19 antibody, an anti-CEA antibody and fragments thereof. The target cell may be a cancer cell. The cell surface molecule may be a tumor associated antigen. The cell surface molecule may be selected from the group consisting of: a cluster of differentiation protein, a receptor, an integral membrane protein and a glycoprotein. The homogeneity of the chimeric antigen receptor-effector cell switch may be at least about 90%.

[0006] Further disclosed herein are pharmaceutical compositions comprising: a chimeric antigen receptor-effector cell switch comprising: a peptidic antigen that binds a chimeric antigen receptor on an effector cell; and a targeting moiety that binds a cell surface molecule on a target; and a pharmaceutically acceptable salt, excipient and/or vehicle.

[0007] Disclosed herein are kits comprising: a chimeric antigen receptor-effector cell switch comprising: a peptidic antigen that binds a chimeric antigen receptor on an effector cell; and a targeting moiety that binds a cell surface molecule on a target cell; and a chimeric antigen receptor-effector cell comprising a chimeric antigen receptor that binds to the peptidic antigen of the chimeric antigen receptor-effector cell switch. The targeting moiety may comprise a targeting peptide. The targeting moiety comprises a targeting antibody or antibody fragment. The peptidic antigen is grafted within the targeting moiety. The kit may comprise a first chimeric antigen receptor-effector cell switch and a second chimeric antigen receptor-effector cell switch, wherein the first chimeric antigen receptor-effector cell switch comprises a first peptidic antigen and a first targeting moiety and the second chimeric antigen receptor-effector cell switch comprises a second peptidic antigen and a second targeting moiety. The first peptidic antigen and the second peptidic antigen may be the same. The first targeting moiety may bind a first cell surface molecule on a first target cell and the second targeting moiety may bind a second cell surface molecule on a second target cell, wherein the first cell surface molecule and the second cell surface molecule are different. The effector cell may be selected from a T cell, an effector B cell, a natural killer cell, a macrophage and a progenitor thereof. The effector cell may be selected from a naive T cell, a memory stem cell T cell, a central memory T cell, an effector memory T cell, a helper T cell, a CD4+ T cell, a CD8+ T cell, a CD8/CD4+ T cell, an αβ T cell, a γδ T cell, a cytotoxic T cell, a natural killer T cell, a natural killer cell, a macrophage.

[0008] Further disclosed herein are chimeric antigen receptors that bind a peptidic antigen of a chimeric antigen receptor-effector cell switch. The chimeric antigen receptor may comprise an antibody or antibody fragment that binds the peptidic antigen of a chimeric antigen receptor-effector cell switch. The antibody fragment or antibody fragment may bind a eukaryotic antigen. The antibody or antibody fragment may bind a non-naturally occurring peptide. The antibody fragment may be an scFv. The antibody or antibody fragment may be selected from an anti-yeast transcription factor GCN4 antibody, an anti-FLAG® antibody, an anti-HTP antibody and fragments thereof. The chimeric antigen receptor may be encoded by a polynucleotide based on or derived from SEQ ID NO: 1.

[0009] Disclosed herein are effector cells comprising a chimeric antigen receptor, wherein the chimeric antigen receptor that binds a peptidic antigen of a chimeric antigen receptor-effector cell switch. The effector cells may be T cells. The effector cells may comprise one or more polynucleotides based on or derived from SEQ ID NO: 1.

[0010] Further disclosed herein are vectors comprising a polynucleotide having a sequence that encodes a chimeric antigen receptor-effector cell switch, wherein the chimeric antigen receptor-effector cell switch comprises peptidic antigen and a targeting moiety, wherein the targeting moiety comprises a peptide and binds a cell surface molecule on a target cell.

[0011] Disclosed herein are vectors comprising a first polynucleotide having a first sequence that encodes a heavy chain of a targeting antibody or antibody fragment; a second polynucleotide having a second sequence that encodes a light chain of a targeting antibody or antibody fragment; and a third polynucleotide having a third sequence that encodes a peptidic antigen, wherein expression of the vector produces a chimeric antigen receptor-effector cell switch. The third sequence may be adjacent to a sequence selected from the first sequence and the second sequence. The third sequence may be located within a

sequence selected from the first sequence and the second sequence.

[0012] Further disclosed herein are methods of producing a chimeric antigen receptor-effector cell switch, comprising expressing from one or more polynucleotide vectors: a first sequence that encodes a heavy chain of a targeting antibody or antibody fragment; a second sequence that encodes a light chain of a targeting antibody or antibody fragment; and a third sequence that encodes a peptidic antigen, wherein expression of the vector produces a chimeric antigen receptor- effector cell switch.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] FIG. **1**A illustrates a general overview of chimeric antigen receptor-T cell (CAR T-cell) and CAR T-cell switch therapy with switches disclosed herein. Lymphocytes are isolated from a subject and an expression vector encoding a chimeric antigen receptor is subsequently introduced to the lymphocytes to produce chimeric antigen receptor expressing cells. Resulting engineered lymphocytes are administered to the subject, along with a CAR T-cell switch.

[0014] FIG. **1**B illustrates a CAR T-cell switch, comprising a peptide that is bound by the chimeric antigen receptor of the CAR T-cell and a targeting antibody that is selective for a target cell. Binding of the CAR T-cell switch to the CAR T-cell induces an immune response that would be cytotoxic to the malignant cell also bound to the CAR T-cell switch.

[0015] FIG. **2** depicts a PDB 1P4B crystal structure of an affinity matured scFv (light and medium gray represent light chain and heavy chain) bound to a peptide derived from the yeast transcription factor GCN4 (7P-14P) (dark grey represents the GCN4 peptide).

[0016] FIG. **3** shows mass spectrometry of an anti-CD19-Fab- $GCN4_{CL1}$ CAR-EC switch. Calculated: 49533, found: 49537.09.

[0017] FIG. **4** shows cytotoxicity of an anti-GCN4 CAR T-cell with various anti-CD19 antibodies or antibody fragments with a GCN4 peptide grafted or fused to various regions or domains of the anti-CD19 antibodies or antibody fragments.

[0018] FIG. **5**A shows a non-reducing SDS-PAGE gel of anti-CD19 antibodies or antibody fragments with a GCN4 peptide grafted or fused to various regions or domains of the antibodies or antibody fragments.

[0019] FIG. **5**B shows a reducing SDS-PAGE gel of anti-CD19 antibodies or antibody fragments with a GCN4 peptide grafted or fused to various regions or domains of the antibodies or antibody fragments.

[0020] FIG. **6** depicts a yeast GCN4 peptide grafting positions in an anti-CD19 Fab (FMC63).

[0021] FIG. **7** shows in vivo efficacy of an anti-CD19 Fab - GCN4 peptide CAR T-cell switch and an anti-GCN4 CAR T-cell in a xenograft tumor mouse model. FIG. **7**A shows quantification of tumors in untreated versus treated mice. FIG. **7**B depicts in vivo treatment regimen and visualization of tumor cells in untreated versus treated mice.

[0022] FIG. **8** shows cytotoxicity of an anti-GCN4 CAR T-cell and CAR T-cell switch (anti-BCMA antibody -GCN4 peptide grafted into the light chain constant domain) against BCMA-positive cells (OPM2).

DETAILED DESCRIPTION OF THE INVENTION

[0023] Current chimeric antigen receptor T cell (CAR T-cell) therapies can be unreliable due to lack of means to control CAR T-cell activity. Disclosed herein are compositions and methods for selectively activating and deactivating chimeric antigen receptor T cells, which may provide for safer and more versatile immunotherapies than those currently being tested and administered. Disclosed herein are switchable chimeric antigen receptor effector cells (CAR-ECs) and chimeric antigen receptor effector cell (CAR-EC) switches, wherein the CAR-EC switches have a first region that is bound by a chimeric antigen receptor on the CAR-EC and a second region that binds a cell surface molecule on target cell, thereby stimulating an immune response from the CAR-EC that is cytotoxic to the bound target cell. In general, the CAR-EC is a T cell. In this way, the CAR-EC switch may act as an "on-switch" for CAR-EC activity. Activity may be "turned off" by reducing or ceasing administration of the switch. These CAR-EC switches may be used with CAR-ECs disclosed herein, as well as existing CAR T-cells, for the treatment of a disease or condition, such as cancer, wherein the target cell is a malignant cell. Such treatment may be referred to herein as switchable immunotherapy, for which an exemplary schematic overview is depicted in FIG. **1**.

[0024] The CAR-EC switches disclosed herein comprise a first region that binds a cell surface molecule on a target cell, and a second region that is bound by a chimeric antigen receptor. In general the first region is a targeting polypeptide. The targeting polypeptide may be a targeting antibody or antibody fragment that binds an antigen on the target cell. Alternatively or additionally, the first region may comprise a non-peptide small molecule (e.g. vitamin, metabolite). The second region, referred to herein as a chimeric antigen binding peptidic antigen (CAR-BP), comprises a peptide. For simplicity, the term chimeric antigen binding peptidic antigen may simply be referred to herein as a peptidic antigen. In general, the CAR-BP is fused to a terminus of the targeting polypeptide or grafted within the targeting polypeptide. Fusing or grafting the CAR-BP to the targeting polypeptide may be carried out by cloning one or more polynucleotides encoding the first region and the second region into a polynucleotide expression vector, in a desired order or combination.

[0025] Methods of treating a disease or condition comprising administering the CAR-EC switches, disclosed herein, may provide for a titratable response, improved safety and/or cessation of CAR-EC activity by reducing or ceasing administration of the CAR-EC switch. In contrast to other approaches of controlling CAR-EC activity, which "turn off" CAR-EC activity by competing with the target cell surface molecule for binding the CAR, the CAR-EC switches disclosed herein, generally function as CAR-EC activators or "on" switches.

[0026] Further disclosed herein are CAR-EC platforms including CAR-EC switches and effector cells comprising universal chimeric antigen receptors (CAR) that can bind multiple CAR-EC switches, providing for sequential targeting of one or more types of target cells (e.g. treatment of heterogeneous tumors). The CAR may comprise an ultra-high affinity antibody or antibody fragment (e.g. scFv) to the switch. Methods of producing the CAR-EC switches disclosed herein may advantageously provide for control of

CAR-EC cell activity, titration of off-target reactivity, abrogation of tumor lysis syndrome (TLS), attenuation of cytokine release syndrome (CRS), and/or optimization of CAR-EC switch binding by affinity, valency, geometry, length and/or chemistry through site-specific grafting/fusing of CAR-EC switch peptides/antibodies.

[0027] Unless otherwise specified, the terms "switch" and "CAR-EC switch", as used herein, are used interchangeably and may refer to a peptide switch. The antibody portion of the peptide antibody switch may comprise at least a portion of an antibody or an entire antibody. For example, the antibody portion of the peptide antibody switch may comprise at least a portion of a heavy chain, a portion of a light chain, a portion of a variable region, a portion of a constant region, a portion of a complementarity determining region (CDR), or a combination thereof. The antibody portion of the peptide antibody switch and/or hapten antibody switch may comprise at least a portion of the Fc (fragment, crystallizable) region. The antibody portion of the peptide antibody switch may comprise at least a portion of the complementarity determining region (e.g., CDR1, CDR2, CDR3). The antibody portion of the peptide antibody switch may comprise at least a portion of the Fab (fragment, antigen-binding) region. The peptide switch may be a peptide-Fab switch.

[0028] Before the present methods, kits and compositions are described in greater detail, it is to be understood that this invention is not limited to particular method, kit or composition described, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims. Examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the present invention, and are not intended to limit the scope of what the inventors regard as their invention nor are they intended to represent that the experiments below are all or the only experiments performed. Efforts have been made to ensure accuracy with respect to numbers used (e.g. amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

[0029] Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limits of that range is also specifically disclosed. Each smaller range between any stated value or intervening value in a stated range and any other stated or intervening value in that stated range is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included or excluded in the range, and each range where either, neither or both limits are included in the smaller ranges is also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the invention.

[0030] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, some potential and preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited. It is understood that the present disclosure supersedes any disclosure of an incorporated publication to the extent there is a contradiction.

[0031] As will be apparent to those of skill in the art upon reading this disclosure, each of the individual embodiments described and illustrated herein has discrete components and features which may be readily separated from or combined with the features of any of the other several embodiments without departing from the scope or spirit of the present invention. Any recited method can be carried out in the order of events recited or in any other order which is logically possible.

[0032] It must be noted that as used herein and in the appended claims, the singular forms "a", "an", and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a cell" includes a plurality of such cells and reference to "the peptide" includes reference to one or more peptides and equivalents thereof, e.g. polypeptides, known to those skilled in the art, and so forth.

[0033] The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided may be different from the actual publication dates which may need to be independently confirmed.

[0034] Methods, kits and compositions are provided for producing CAR-EC platforms and CAR-EC switches used to bring an effector cell together with a target in a subject. These methods, kits and compositions find therapeutic use in a number of diseases. For example, heterogeneous tumors and blood cell malignancies (e.g. acute lymphoblastic leukemia and chronic lymphocytic leukemia) may be more effectively treated with a CAR-EC platform when the length, valency and orientation of the CAR-EC switch linkage as well as the CAR-EC switch cell targeting moiety is optimized. Heterogeneous tumors may be more effectively treated with multiple CAR-EC switches that target more than one tumor antigens. Advantages, and features of the invention will become apparent to those persons skilled in the art upon reading the details of the compositions and methods as more fully described below.

[0035] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

IA. Peptide Switch

[0036] Disclosed herein are chimeric antigen receptor-effector cell switches comprising: a peptidic antigen that binds a chimeric antigen receptor on an effector cell; and a targeting moiety that binds a cell surface molecule on a target. The targeting moiety may be a targeting polypeptide, comprising a targeting peptide that binds the cell surface molecule. The targeting moiety may be a targeting antibody or antibody fragment comprising the targeting peptide, wherein the targeting peptide is an antigen binding site of the targeting antibody or antibody fragment. The targeting peptide may be at least a portion of an antibody fragment and the cell surface molecule may be an antigen. The targeting moiety may comprise one or more peptides that recognize and/or bind one or more antigens. The targeting moiety may comprise one or more peptides that recognize and/or bind only one antigen. The peptidic antigen may not comprise an antibody or antibody fragment that recognizes and/or binds an antigen.

[0037] Further disclosed herein are CAR-EC switches comprising: a peptidic antigen that binds a CAR (CAR-BP) on an effector cell, wherein the CAR-BP; and a targeting polypeptide that binds a cell surface molecule on a target cell. The peptidic antigen may be fused to a terminus of the targeting polypeptide. The peptidic antigen may be grafted into the targeting polypeptide (e.g. between chosen amino acids of the targeting polypeptide). The targeting polypeptide may be fused to a terminus of the peptidic antigen. The targeting polypeptide may be grafted into the peptidic antigen (e.g. between chosen amino acids of the peptidic antigen).

[0038] Disclosed herein are CAR-EC switches comprising: a peptidic antigen that binds a CAR (CAR-BP) on an effector cell; and a targeting antibody or antibody fragment that binds an antigen on a target. The targeting antibody or antibody fragment may be selected from an immunoglobulin, a Fab, a Fab′, a $F(ab')_2$ and an scFv. The targeting antibody or antibody fragment may comprise a light chain. The targeting antibody or antibody fragment may comprise a heavy chain.

[0039] The peptidic antigen may be fused to an N terminus of the light chain of the targeting antibody or antibody fragment. The peptidic antigen may be fused to a C terminus of the light chain of the targeting antibody or antibody fragment. The peptidic antigen may be fused to an N terminus of the heavy chain of the targeting antibody or antibody fragment. The peptidic antigen may be fused to a C terminus of the heavy chain of the targeting antibody or antibody fragment. The peptidic antigen may be fused to an N terminus of a VL domain of the targeting antibody or antibody fragment. The peptidic antigen may be fused to an N terminus of a VH domain of the targeting antibody or antibody fragment. The peptidic antigen may be fused to a C terminus of a CL domain of the targeting antibody or antibody fragment. The peptidic antigen may be fused to a C terminus of an Fc domain of the targeting antibody or antibody fragment. The peptidic antigen may be fused to an N terminus of a VL domain of an IgG. The peptidic antigen may be fused to an N terminus of a VH domain of an IgG. The peptidic antigen may be fused to a C terminus of a CL domain of an IgG. The peptidic antigen may be fused to a C terminus of an Fc domain of an IgG. The peptidic antigen may be fused to an N terminus of a VL domain of a Fab. The peptidic antigen may be fused to an N terminus of a VH domain of a Fab. The peptidic antigen may be fused to a C terminus of a CL domain of a Fab. The peptidic antigen may be fused to a C terminus of a CH_1 domain of the Fab.

[0040] The peptidic antigen may be grafted into an internal site of a targeting antibody or antibody fragment (e.g. between chosen amino acids of the targeting antibody or antibody fragment). The peptidic antigen may be grafted into a heavy chain of a targeting antibody or antibody fragment. The peptidic antigen may be grafted into a light chain of a targeting antibody or antibody fragment. The peptidic antigen may be grafted into a constant domain/region of a targeting antibody or antibody fragment. The peptidic antigen may be grafted into a variable domain/region of a targeting antibody or antibody fragment. The peptidic antigen may be grafted into an internal site of a Fab. The peptidic antigen may be grafted into an internal site of an immunoglobulin (e.g. IgG). The peptidic antigen may be grafted into a domain of the targeting antibody or fragment thereof selected from a CL domain, a CH_1 domain, a CH_2 domain, a CH_3 domain, a VL domain, a VH domain and a hinge domain. The peptidic antigen may be grafted between two domains of the antibody or fragment thereof selected from a CL domain, a CH_1 domain, a CH_2 domain, a CH_3 domain, a VL domain, a VH domain and a hinge domain, wherein the two domains are adjacent. The peptidic antigen may be grafted into a CL domain of the antibody or fragment thereof. The peptidic antigen may be grafted into a CH_1 domain of the antibody or fragment thereof. The peptidic antigen may be grafted into a hinge domain of the antibody or fragment thereof. The peptidic antigen may be grafted into a loop of the antibody or fragment thereof. The peptidic antigen may be grafted into a CL domain loop of the antibody or fragment thereof.

[0041] The CAR-BP may be grafted into the C terminus of the antibody or antibody fragment and therefore the distance between the chimeric antigen receptor and the target may differ substantially depending on the size of CAR-EC switch (approximately 40 Å for scFv, 70 Å for Fab, and 120 Å for IgG). While a larger distance may negatively impact efficacy in vitro, the increased residence time of the full length antibody may be superior in vivo.

[0042] The CAR-BP may further comprise a linker. The linker may provide the CAR-EC switch flexibility, length or geometry optimal for facilitating an interaction or effect of the CAR-EC on the target cell. The CAR-BP may further comprise one or more linkers. The CAR-BP may comprise two linkers. The linker may comprise a peptide. The linker may be at least about 1, at least about 2, at least about 3, at least about 4, at least about 5, at least about 6, at least about 7, at least about 8, at least about 9 or at least about 10 amino acids in length. The one or more linkers may comprise about 5, about 10, about 15, about 20, about 25, about 30, about 35, about 40, about 45, about 50, about 55, about 60, about 70, about 80, about 90 or about 100 amino acids. The linker may be located at the N terminus or the C terminus of the CAR-BP to graft the CAR-BP to the targeting polypeptide. A first linker may be fused to the N terminus of the CAR-BP and a second linker may be fused to the C terminus of the CAR-BP. The linker may be comprised of the sequence $(GGGGS)_n$, (SEQ ID NO.40), wherein n may be 1, 2, 3, 4, 5 or more. The linker may be comprised of the sequence $(GGS)_n$, (SEQ ID NO.40), wherein n may be 1, 2, 3, 4, 5 or more. The CAR-BP may be grafted into an internal site of

the targeting polypeptide with a linker on either end of the CAR-BP. The linker may comprise a sequence selected from SEQ ID NOS: 40-44.

The Peptidic Antigen

[0043] The peptidic antigen (CAR-BP) may be a peptide that is bound by a chimeric antigen receptor (CAR). The peptidic antigen may have high proteolytic stability and low immunogenicity in humans relative to peptides in general. The CAR-BP may be selected from a hormone, a cytokine, a chemokine, a growth factor, a cell adhesion molecule, a signaling peptide, a receptor, a cell surface peptide and fragments thereof. The CAR-BP may be a peptoid. The CAR-BP may be a peptide nucleic acid (PNA). The CAR-BP may be a ligand or a fragment thereof. The ligand may be a hormonal ligand. The ligand may be a peptide ligand. The CAR-BP may be a cyclic peptide. The CAR-BP may be a linear peptide. The CAR-BP may have a length of between about 2 and about 10, about 10 and about 20, about 20 and about 30, about 30 and about 40, about 40 and about 50, about 50 and about 60, about 60 and about 70, about 70 and about 80, and about 80 and about 90 amino acids. The CAR-BP may be an antigen. The CAR-BP may be an epitope. The CAR-BP may be a nonlinear epitope. The CAR-BP may further comprise a second peptide.

[0044] The peptidic antigen may not comprise an antibody or antibody fragment. The peptidic antigen may comprise less than 10 amino acids of an antibody or antibody fragment. The peptidic antigen may comprise less than 12 amino acids of an antibody or antibody fragment. The peptidic antigen may comprise less than 15 amino acids of an antibody or antibody fragment. The peptidic antigen may comprise less than 20 amino acids of an antibody or antibody fragment. The peptidic antigen may comprise less than 22 amino acids of an antibody or antibody fragment. The peptidic antigen may comprise less than 30 amino acids of an antibody or antibody fragment. The peptidic antigen may not comprise a paratope of an antibody or antibody fragment.

[0045] Disclosed herein are chimeric antigen receptor effector cell switches comprising a targeting moiety and a peptidic antigen, wherein the targeting moiety is a targeting polypeptide. The targeting polypeptide may comprise a targeting antibody or antibody fragment. The targeting antibody or antibody fragment may comprise a variable domain. The variable domain may be selected from a VH domain and a VL domain. The peptidic antigen may not be located at or near the N terminus of the VH domain. The peptidic antigen may not be located at or near the N terminus of the VL domain.

[0046] The peptidic antigen may comprise a non-naturally occurring peptide. The peptidic antigen may comprise a synthetic peptide. The peptidic antigen may comprise a non-animal peptide (e.g. a peptide not expressed in an animal). The peptidic antigen may comprise a non-mammalian peptide. The peptidic antigen may comprise a non-human peptide. The peptide may comprise a peptide derived from a plant, a yeast, a bacteria, a reptile, a bird or an insect.

[0047] The peptidic antigen may comprise a myc-tag. The peptidic antigen may comprise His-tag. The peptidic antigen may comprise an HA-tag. The peptidic antigen may comprise peridinin chlorophyll protein complex. The peptidic antigen may comprise green fluorescent protein (GFP). The peptidic antigen may comprise red fluorescent protein (RFP). The peptidic antigen may comprise phycoerythrin (PE). The peptidic antigen may comprise streptavidin. The peptidic antigen may comprise avidin. The peptidic antigen may comprise horse radish peroxidase (HRP). The peptidic antigen may comprise alkaline phosphatase. The peptidic antigen may comprise glucose oxidase. The peptidic antigen may comprise glutathione-S-transferase (GST). The peptidic antigen may comprise maltose binding protein. The peptidic antigen, by non-limiting example, may be a c-myc tag, polyhistidine tag, V5, VSVG, softag 1, softag 3, express tag, S tag,palmitoylation, nitrosylation, SUMO tag, thioredoxin, poly(NANP), poly-Arg, calmodulin binding protein, PurF fragment, ketosteroid isomerase, PaP3.30, TAF12 histone fold domain, FKBP-tag, SNAP tag, Halo-tag, peptides from RNAse I. The peptidic antigen may comprise a protease cleavage site. The protease cleavage site may be recognized by thrombin, factor Xa, TEV protease or enterokinase.

[0048] The peptidic antigen may be a small linear hydrophilic peptide. The small linear hydrophilic peptide may comprise a linker. The small linear hydrophilic peptide may be a hydrophilic target peptide (HTP). The small linear hydrophilic peptide may comprise the sequence GGGGSDYKDDDDK (SEQ ID NO: 5). The small linear hydrophilic peptide may comprise the sequence GGGGSDYKDDDDKP (SEQ ID NO: 6). The small linear hydrophilic peptide may consist essentially of the sequence GGGGSDYKDDDDK (SEQ ID NO: 5). The small linear hydrophilic peptide may consist essentially of the sequence GGGGSDYKDDDDKP (SEQ ID NO: 6). The small linear hydrophilic peptide may be at least about 50% homologous to SEQ ID NOs: 5 or 6. The small linear hydrophilic peptide may be at least about 60% homologous to SEQ ID NOs: 5 or 6. The small linear hydrophilic peptide may be at least about 70% homologous to SEQ ID NOs: 5 or 6. The small linear hydrophilic peptide may be at least about 80% homologous to SEQ ID NOs: 5 or 6. The small linear hydrophilic peptide may be at least about 85% homologous to SEQ ID NOs: 5 or 6. The small linear hydrophilic peptide may be at least about 90% homologous to SEQ ID NOs: 5 or 6. The small linear hydrophilic peptide may have reduced non-specific binding relative to other peptides known in the art. The small linear hydrophilic peptide may have reduced non-specific binding and reduced fusion protein instability relative to other peptides disclosed herein. The peptidic antigen may comprise a FLAG® tag (SEQ ID NO: 7) or a derivative or a homolog thereof.

[0049] The peptide may be based on or derived from a naturally occurring peptide. The peptide may be based on or derived from a human peptide. The peptide may be based on or derived from an peptide expressed in animal selected from a chimpanzee, a monkey, a rat, a mouse, a bird, a fish, a pig, a horse, a cow, a goat, a chicken, a rabbit and a guinea pig. The peptide may be based on or derived from a mammalian peptide. The peptide may be based on or derived from a non-mammalian peptide. The peptide may be based on or derived from a peptide expressed in a plant. The peptide may be based on or derived from a peptide expressed in a bacterium. The peptide may be based on or derived from a prokaryotic peptide. The peptide may be based on or derived from a eukaryotic peptide. The peptide may be based on or derived from a peptide expressed by a yeast.The peptidic antigen may comprise a yeast transcrip-

tion factor GCN4 peptide or a derivative or a homolog thereof. The yeast transcription factor GCN4 peptide may comprise the sequence RMKQLEPKVEELLPKNYHLENEVARLKKLVGER (SEQ ID NO: 2). The yeast transcription factor GCN4 peptide may comprise the sequence NYHLENEVARLKKL (SEQ ID NO: 3). The yeast transcription factor GCN4 peptide may consist essentially of the sequence RMKQLEPKVEELLPKNYHLENEVARLKKLVGER (SEQ ID NO: 2). The yeast transcription factor GCN4 peptide may consist essentially of the sequence NYHLENEVARLKKL (SEQ ID NO: 3). The yeast transcription factor GCN4 peptide may comprise a portion of SEQ ID NO. 2. The portion of SEQ ID NO. 2 may be at least 4 amino acids long. The portion of SEQ ID NO. 2 may be about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12 or about 13 amino acids long. The yeast transcription factor GCN4 peptide may be at least about 50% homologous to SEQ ID NOs: 2 or 3. The yeast transcription factor GCN4 peptide may be at least about 60% homologous to SEQ ID NOs: 2 or 3. The yeast transcription factor GCN4 peptide may be at least about 70% homologous to SEQ ID NOs: 2 or 3. The yeast transcription factor GCN4 peptide may be at least about 80% homologous to SEQ ID NOs: 2 or 3. The yeast transcription factor GCN4 peptide may be at least about 85% homologous to SEQ ID NOs: 2 or 3. The yeast transcription factor GCN4 peptide may be at least about 90% homologous to SEQ ID NOs: 2 or 3. The CAR-EC switch may comprise a yeast GCN4 peptide and one or more linkers. The CAR-EC switch may comprise SEQ ID NO. 4.

The Targeting Moiety

[0050] The targeting moiety may bind to a cell surface molecule on a target. The cell surface molecule may comprise an antigen. The cell surface molecule may be selected from a protein, a lipid moiety, a glycoprotein, a glycolipid, a carbohydrate, a polysaccharide, a nucleic acid, an MHC-bound peptide, or a combination thereof. The cell surface molecule may comprise parts (e.g., coats, capsules, cell walls, flagella, fimbrae, and toxins) of bacteria, viruses, and other microorganisms. The cell surface molecule may be expressed by the target cell. The cell surface molecule may not be expressed by the target cell. By way of non-limiting example, the cell surface molecule may be a ligand expressed by a cell that is not the target cell and that is bound to the target cell or a cell surface molecule of the target cell. Also, by non-limiting example, the cell surface molecule may be a toxin, exogenous molecule or viral protein that is bound to a cell surface or cell surface receptor of the target cell.

[0051] The targeting polypeptide may be a targeting antibody or antibody fragment. The targeting antibody or antibody fragment may be an immunoglobulin (Ig). The immunoglobulin may selected from an IgG, an IgA, an IgD, an IgE, an IgM, a fragment thereof or a modification thereof. The immunoglobulin may be IgG. The IgG may be IgG1. The IgG may be IgG2. The IgG may have one or more Fc mutations for modulating endogenous T cell FcR binding to the CAR-EC switch. The IgG may have one or more Fc mutations for removing the Fc binding capacity to the FcR of FcR-positive cells. Removal of the Fc binding capacity may reduce the opportunity for crosslinking of the CAR-EC to FcR positive cells, wherein crosslinking of the CAR-EC to FcR positive cells would activate the CAR-EC in the absence of the target cell. As such, modulating the endogenous T cell FcR binding to the CAR-EC switch may reduce an ineffective or undesirable immune response. The one or more Fc mutations may remove a glycosylation site. The one or more Fc mutations may be selected from E233P, L234V, L235A, delG236, A327G, A330S, P331S, N297Q and any combination thereof. The one or more Fc mutations may be in IgG1. The one or more Fc mutations in the IgG1 may be L234A, L235A, or both. Alternatively, or additionally, the one or more Fc mutations in the IgG1 may be L234A, L235E, or both. Alternatively, or additionally, the one or more Fc mutations in the IgG1 may be N297A. Alternatively, or additionally, the one or more mutations may be in IgG2. The one or more Fc mutations in the IgG2 may be V234A, V237A, or both.

[0052] The targeting antibody or antibody fragment may be an Fc null immunoglobulin or a fragment thereof.

[0053] As used herein, the term "antibody fragment" refers to any form of an antibody other than the full-length form. Antibody fragments herein include antibodies that are smaller components that exist within full-length antibodies, and antibodies that have been engineered. Antibody fragments include, but are not limited to, Fv, Fc, Fab, and (Fab')2, single chain Fv (scFv), diabodies, triabodies, tetrabodies, bifunctional hybrid antibodies, CDR1, CDR2, CDR3, combinations of CDRs, variable regions, framework regions, constant regions, heavy chains, light chains, alternative scaffold non-antibody molecules, and bispecific antibodies. Unless specifically noted otherwise, statements and claims that use the term "antibody" or "antibodies" may specifically include "antibody fragment" and "antibody fragments."

[0054] The targeting antibody fragment may be human, fully human, humanized, human engineered, non-human, and/or chimeric antibody. The non-human antibody may be humanized to reduce immunogenicity to humans, while retaining the specificity and affinity of the parental non-human antibody. Chimeric antibodies may refer to antibodies created through the joining of two or more antibody genes which originally encoded for separate antibodies. A chimeric antibody may comprise at least one amino acid from a first antibody and at least one amino acid from a second antibody, wherein the first and second antibodies are different. At least a portion of the antibody or antibody fragment may be from a bovine species, a human species, or a murine species. At least a portion of the antibody or antibody fragment may be from a rat, a goat, a guinea pig or a rabbit. At least a portion of the antibody or antibody fragment may be from a human. At least a portion of the antibody or antibody fragment antibody may be from cynomolgus monkey.

[0055] The targeting antibody or antibody fragment may be based on or derived from an antibody or antibody fragment from a mammal, bird, fish, amphibian, reptile. Mammals include, but are not limited to, carnivores, rodents, elephants, marsupials, rabbits, bats, primates, seals, anteaters, cetaceans, odd-toed ungulates and even-toed ungulates. The mammal may be a human, non-human primate, mouse, sheep, cat, dog, cow, horse, goat, or pig.

[0056] The targeting antibody or an antibody fragment may target an antigen selected from, by non-limiting example, CD19, Her2, CLL-1, CD33, EGFRvIII, CD20, CD22, BCMA or a fragment thereof. The antigen may comprise a

wildtype antigen. The antigen may comprise one or more mutations.

[0057] The targeting antibody or antibody fragment may be an anti-CD19 antibody or a fragment thereof. The targeting polypeptide may be an anti-CD22 antibody. The targeting polypeptide may be an anti-BCMA antibody or a fragment thereof. The targeting polypeptide may be an anti-CS1 antibody or a fragment thereof. The targeting polypeptide may be an anti-EGFRvIII antibody or a fragment thereof. The targeting polypeptide may be an anti-Her2 antibody or a fragment thereof. The targeting polypeptide may comprise an anti-CD20 antibody or antibody fragment. The targeting polypeptide may comprise rituximab. The targeting polypeptide may comprise an anti-EGFR antibody or antibody fragment. The targeting polypeptide may comprise an anti-CEA antibody or antibody fragment. The targeting polypeptide may comprise an anti-CLL-1 antibody or antibody fragment. The targeting polypeptide may comprise an anti-CD33 antibody or antibody fragment. The targeting polypeptide may not comprise an anti-EpCAM antibody or fragment thereof.

[0058] The targeting antibody or antibody fragment may be selected any commercially available antibody. The targeting antibody or antibody fragment may be selected from ado-trastuzumab emtansine, alemtuzumab, bevacizumab, brentuximab, vedotin, gemtuzumab, ozogamicin, ipilimumab, ibritumomab, tiuxetan, panitumumab, cetuximab, erbitux, rituximab, trastuzumab and fragments thereof.

[0059] The targeting antibody or antibody fragment may comprise an anti-CD19 antibody or fragment thereof. The targeting antibody or fragment thereof may comprise a light chain of the anti-CD19 antibody or fragment thereof. The light chain of the anti-CD19 antibody or fragment thereof may be encoded by a nucleotide sequence based on or derived from SEQ ID NO. 8. The nucleotide sequence may be about 99%, about 98%, about 97%, about 96%, about 95%, about 92%, about 90%, about 85%, about 80%, about 75%, about 70%, about 65%, about 60%, about 55%, about 50%, about 45%, about 40%, about 35%, about 30%, about 25%, about 20%, about 15%, about 10%, about 5% or about 2% homologous to SEQ ID NO. 8. The targeting antibody or fragment thereof may comprise a heavy chain of the anti-CD19 antibody or fragment thereof. The heavy chain of the anti-CD19 antibody or fragment thereof may be encoded by a sequence based on or derived from SEQ ID NO. 9. The nucleotide sequence may be about 99%, about 98%, about 97%, about 96%, about 95%, about 92%, about 90%, about 85%, about 80%, about 75%, about 70%, about 65%, about 60%, about 55%, about 50%, about 45%, about 40%, about 35%, about 30%, about 25%, about 20%, about 15%, about 10%, about 5% or about 2% homologous to SEQ ID NO. 9.

[0060] The targeting antibody or antibody fragment may comprise an anti-CD19 antibody or fragment thereof. The targeting antibody or fragment thereof may comprise a light chain of the anti-CD19 antibody or fragment thereof. The light chain of the anti-CD19 antibody or fragment may comprise an amino acid sequence based on or derived from SEQ ID NO. 27. The amino acid sequence may be about 99%, about 98%, about 97%, about 96%, about 95%, about 92%, about 90%, about 85%, about 80%, about 75%, about 70%, about 65%, about 60%, about 55%, about 50%, about 45%, about 40%, about 35%, about 30%, about 25%, about 20%, about 15%, about 10%, about 5% or about 2% homologous to SEQ ID NO. 27. The targeting antibody or fragment thereof may comprise a heavy chain of the anti-CD19 or fragment thereof. The targeting antibody or fragment thereof may comprise a heavy chain of an anti-CD19 IgG. The heavy chain of the anti-CD19 IgG may comprise a sequence based on or derived from SEQ ID NO. 28. The amino acid sequence may be about 99%, about 98%, about 97%, about 96%, about 95%, about 92%, about 90%, about 85%, about 80%, about 75%, about 70%, about 65%, about 60%, about 55%, about 50%, about 45%, about 40%, about 35%, about 30%, about 25%, about 20%, about 15%, about 10%, about 5% or about 2% homologous to SEQ ID NO. 28. The targeting antibody or fragment thereof may comprise a heavy chain of an anti-CD19 Fab. The heavy chain of the anti-CD19 Fab may comprise a sequence based on or derived from SEQ ID NO. 29. The amino acid sequence may be about 99%, about 98%, about 97%, about 96%, about 95%, about 92%, about 90%, about 85%, about 80%, about 75%, about 70%, about 65%, about 60%, about 55%, about 50%, about 45%, about 40%, about 35%, about 30%, about 25%, about 20%, about 15%, about 10%, about 5% or about 2% homologous to SEQ ID NO. 29.

[0061] The targeting antibody or antibody fragment may comprise a nucleotide sequence selected from SEQ ID NOs: 8-20. The targeting polypeptide may be based on or derived from a nucleotide selected from SEQ ID NOs: 8-20. The targeting antibody or antibody fragment may comprise an amino acid sequence selected from SEQ ID NOs: 21-29. The targeting polypeptide may be based on or derived from an amino acid sequence selected from SEQ ID NOs: 21-29.

[0062] Disclosed herein are chimeric antigen receptor effector cell (CAR-EC) switches comprising a peptidic antigen and a targeting moiety that binds a cell surface molecule on a target cell. Generally, binding of the effector cell and the target cell to the CAR-EC switch construct brings the target cell into proximity with the effector cell sufficiently close for an activity of the effector cell to have an effect on the target cell. For example, when the T cell and the target cell are bound to the CAR-EC switch, the T cell may produce an immune response that has a cytotoxic effect on the target cell.

[0063] The CAR-EC switches may interact with a plurality of target cells. The target cell may be an infected cell. The target cell may be a pathogenically infected cell. The target cell may be a diseased cell. The target cell may be a genetically-modified cell. The target cell may not be a host cell. The target cell may come from an invading organism (e.g. yeast, worm, bacteria, fungus). Further disclosed herein are CAR-EC switches that interact with a molecule on a non-cell target. The non-cell target may be a virus or a portion thereof. The non-cell target may be a fragment of a cell. The non-cell target may be an extracellular matrix component or protein.

[0064] The target cell may be derived from a tissue. The tissue may be selected from brain, esophagus, breast, colon, lung, glia, ovary, uterus, testes, prostate, gastrointestinal tract, bladder, liver, thymus, bone and skin. The target cell may be derived from one or more endocrine glands. Alternatively, or additionally, the target cell may be derived from one or more endocrine glands. The endocrine gland may be

a lymph gland, pituitary gland, thyroid gland, parathyroid gland, pancreas, gonad or pineal gland.

[0065] The target cell may be selected from a stem cell, a pluripotent cell, a hematopoietic stem cell or a progenitor cell. The target cell may a circulating cell. The target cell may be an immune cell.

[0066] The target cell may be a cancer stem cell. The target cell may be a cancer cell. The cancer cell may be derived from a tissue. The tissue may be selected from, by way of non-limiting example, a brain, an esophagus, a breast, a colon, a lung, a glia, an ovary, a uterus, a testicle, a prostate, a gastrointestinal tract, a bladder, a liver, a thyroid and skin. The cancer cell may be derived from bone. The cancer cell may be derived from blood. The cancer cell may be derived from a B cell, a T cell, a monocyte, a thrombocyte, a leukocyte, a neutrophil, an eosinophil, a basophil, a lymphocyte, a hematopoietic stem cell or an endothelial cell progenitor. The cancer cell be derived from a CD 19-positive B lymphocyte. The cancer cell may be derived from a stem cell. The cancer cell may be derived from a pluripotent cell. The cancer cell may be derived from one or more endocrine glands. The endocrine gland may be a lymph gland, pituitary gland, thyroid gland, parathyroid gland, pancreas, gonad or pineal gland.

[0067] The cancer cell may be a CD19-positive cell. The cancer cell may be a CD19-positive B lymphocyte. The cancer cell may be a Her2-positive cell. The Her2-positive cell may be a Her2-positive breast cancer cell. The target cell may be a BCMA-positive cell. The cancer cell may be a BCMA-positive multiple myeloma cell. The cancer cell may be a CS1-positive cell. The CS1-positive cell may be a multiple myeloma cell. The cancer cell may be a EGFRvIII-positive cell. The cancer cell may be a EGFRvIII-positive glioblastoma cell. The cancer cell may be a CD20-positive cell. The cancer cell may be a CD22-positive cell.

[0068] The cell surface molecule may be an antigen. The antigen may be at least a portion of a surface antigen or a cell surface marker on a cell. The antigen may be a receptor or a co-receptor on a cell. The antigen may refer to a molecule or molecular fragment that may be bound by a major histocompatibility complex (MHC) and presented to a T-cell receptor. The term "antigen" may also refer to an immunogen. The immunogen may provoke an adaptive immune response if injected on its own into a subject. The immunogen may induce an immune response by itself. The antigen may be a superantigen, T-dependent antigen or a T-independent antigen._The antigen may be an exogenous antigen. Exogenous antigens are typically antigens that have entered the body from the outside, for example by inhalation, ingestion, or injection. Some antigens may start out as exogenous antigens, and later become endogenous (for example, intracellular viruses). The antigen may be an endogenous antigen. The endogenous antigen may be an antigen that has been generated within cells as a result of normal cell metabolism, or because of pathogenic infections (e.g., viral, bacterial, fungal, parasitic). The antigen may be an autoantigen. The autoantigen may be a normal protein or complex of proteins (and sometimes DNA or RNA) that is recognized by the immune system of patients suffering from a specific autoimmune disease. These antigens should, under normal conditions, not be the target of the immune system, but, due to genetic and/or environmental factors, the normal immunological tolerance for such an antigen is not present in these patients. The antigen may be present or over-expressed due to a condition or disease. The condition or disease may be a cancer or a leukemia. The condition may be an inflammatory disease or condition. The condition or disease may be a metabolic disease. The condition may be a genetic disorder.

[0069] The cell surface molecule may be an antigen that has been designated as a tumor antigen. Tumor antigens or neoantigens may be antigens that are presented by MHC I or MHC II molecules on the surface of tumor cells. These antigens may sometimes be presented by tumor cells and never by the normal ones. In this case, they are called tumor-specific antigens (TSAs) and, in general, result from a tumor-specific mutation. More common are antigens that are presented by tumor cells and normal cells, and they are called tumor-associated antigens (TAAs). Cytotoxic T lymphocytes that recognize these antigens may be able to destroy the tumor cells before they proliferate or metastasize. Tumor antigens may also be on the surface of the tumor in the form of, for example, a mutated receptor, in which case they may be recognized by B cells. Unless otherwise specified, the terms "tumor antigen," "tumor specific antigen" and "tumor associated antigen," are used interchangeably herein.

[0070] The cell surface molecule may be a receptor. The receptor may be an extracellular receptor. The receptor may be a cell surface receptor. By way of non-limiting example, the receptor may bind a hormone, a neurotransmitter, a cytokine, a growth factor or a cell recognition molecule. The receptor may be a transmembrane receptor. The receptor may be an enzyme-linked receptor. The receptor may be a G-protein couple receptor (GPCR). The receptor may be a growth factor receptor. By way of non-limiting example, the growth factor receptor may be selected from an epidermal growth factor receptor, a fibroblast growth factor receptor, a platelet derived growth factor receptor, a nerve growth factor receptor, a transforming growth factor receptor, a bone morphogenic protein growth factor receptor, a hepatocyte growth factor receptor, a vascular endothelial growth factor receptor, a stem cell factor receptor, an insulin growth factor receptor, a somatomedin receptor, an erythropoietin receptor and homologs and fragments thereof. The receptor may be a hormone receptor. The receptor may be an insulin receptor. By way of non-limiting example, the receptor may selected from an eicosanoid receptor, a prostaglandin receptor, an estrogen receptor, a follicle stimulating hormone receptor, a progesterone receptor, a growth hormone receptor, a gonadotropin-releasing hormone receptor, homologs thereof and fragments thereof. The receptor may be an adrenergic receptor. The receptor may be an integrin. The receptor may be an Eph receptor. The receptor may be a luteinizing hormone receptor. The cell surface molecule may be at least about 50% homologous to a luteinizing hormone receptor. The receptor may be an immune receptor. By way of non-limiting example, the immune receptor may be selected from a pattern recognition receptor, a toll-like receptor, a NOD like receptor, a killer activated receptor, a killer inhibitor receptor, an Fc receptor, a B cell receptor, a complement receptor, a chemokines receptor and a cytokine receptor. By way of non-limiting example, the cytokine receptor may be selected from an interleukin receptor, an interferon receptor, a transforming growth factor receptor, a tumor necrosis factor receptor, a colony stimulating factor receptor, homologs thereof and fragments thereof. The receptor may be a receptor kinase. The receptor kinase may be a tyrosine kinase

receptor. The receptor kinase may be a serine kinase receptor. The receptor kinase may be a threonine kinase receptor. By way of non-limiting example, the receptor kinase may activate a signaling protein selected from a Ras, a Raf, a PI3K, a protein kinase A, a protein kinase B, a protein kinase C, an AKT, an AMPK, a phospholipase, homologs thereof and fragments thereof. The receptor kinase may activate a MAPK/ERK signaling pathway. The receptor kinase may activate Jak, Stat or Smad.

[0071] The cell surface molecule may be a non-receptor cell surface protein. The cell surface molecule may be a cluster of differentiation proteins. By way of non-limiting example, the cell surface molecule may be selected from CD34, CD31, CD117, CD45, CD11b, CD15, CD24, CD114, CD182, CD14, CD11a, CD91, CD16, CD3, CD4, CD25, CD8, CD38, CD22, CD61, CD56, CD30, CD13, CD33, fragments thereof, and homologs thereof.

[0072] The cell surface molecule may be a molecule that does not comprise a peptide. The cell surface molecule may comprise a lipid. The cell surface molecule may comprise a lipid moiety or a lipid group. The lipid moiety may comprise a sterol. The lipid moiety may comprise a fatty acid. The antigen may comprise a glycolipid. The cell surface molecule may comprise a carbohydrate.

[0073] Disclosed herein are CAR-EC switches comprising (a) a chimeric antigen receptor binding peptidic antigen comprising a peptide from a yeast transcription factor peptide; and (b) a targeting polypeptide. The yeast transcription factor peptide may be a GCN4 peptide. The targeting polypeptide may comprise a targeting antibody or antibody fragment. The targeting antibody or antibody fragment may comprise a heavy chain of an antibody. The targeting antibody or antibody fragment may comprise a light chain of an antibody. The targeting antibody or antibody fragment may comprise a Fab of an antibody. The targeting antibody or antibody fragment may comprise an anti-CD19 antibody or a fragment thereof. The targeting antibody or antibody fragment may comprise an anti-Her2 antibody or a fragment thereof. The targeting antibody or antibody fragment may be selected from an anti-CS1 antibody, an anti-BCMA antibody, an anti-EGFRvIII antibody, an anti-CD20 antibody, an anti-EGFR antibody, an anti-CEA antibody, an anti-CLL-1 antibody, an anti-CD33 antibody and fragments thereof.

[0074] Further disclosed herein are CAR-EC switches comprising (a) a CAR binding region comprising a hydrophilic target peptide (HTP) tag; and (b) a targeting polypeptide. The targeting polypeptide may comprise a targeting antibody or antibody fragment. The targeting antibody or antibody fragment may comprise a heavy chain of an antibody. The targeting antibody or antibody fragment may comprise a light chain of an antibody. The targeting antibody or antibody fragment may comprise a Fab of an antibody. The targeting antibody or antibody fragment may comprise an anti-CD19 antibody or a fragment thereof. The targeting antibody or antibody fragment may comprise an anti-Her2 antibody or a fragment thereof. The targeting antibody or antibody fragment may be selected from an anti-CS 1 antibody, an anti-BCMA antibody, an anti-EGFRvIII antibody, an anti-CD20 antibody, an anti-EGFR antibody, an anti-CEA antibody, an anti-CLL-1 antibody, an anti-CD33 antibody and fragments thereof.

[0075] The chimeric antigen receptor-effector cell switch may comprise a heavy chain selected from SEQ ID NO. 32, SEQ ID NO. 33, SEQ ID NO. 34, SEQ ID NO. 35 and SEQ ID NO. 38. The chimeric antigen receptor-effector cell switch may comprise a heavy chain that is at least 50% homologous to a sequence selected from SEQ ID NO. 32, SEQ ID NO. 33, SEQ ID NO. 34, SEQ ID NO. 35 and SEQ ID NO. 38. The chimeric antigen receptor-effector cell switch may comprise a heavy chain that is at least 60% homologous to a sequence selected from SEQ ID NO. 32, SEQ ID NO. 33, SEQ ID NO. 34, SEQ ID NO. 35 and SEQ ID NO. 38. The chimeric antigen receptor-effector cell switch may comprise a heavy chain that is at least 70% homologous to a sequence selected from SEQ ID NO. 32, SEQ ID NO. 33, SEQ ID NO. 34, SEQ ID NO. 35 and SEQ ID NO. 38. The chimeric antigen receptor-effector cell switch may comprise a heavy chain that is at least 80% homologous to a sequence selected from SEQ ID NO. 32, SEQ ID NO. 33, SEQ ID NO. 34, SEQ ID NO. 35 and SEQ ID NO. 38. The chimeric antigen receptor-effector cell switch may comprise a heavy chain that is at least 90% homologous to a sequence selected from SEQ ID NO. 32, SEQ ID NO. 33, SEQ ID NO. 34, SEQ ID NO. 35 and SEQ ID NO. 38.

[0076] The chimeric antigen receptor-effector cell switch may comprise a light chain selected from SEQ ID NO. 30, SEQ ID NO. 31, SEQ ID NO. 36 and SEQ ID NO. 37. The chimeric antigen receptor-effector cell switch may comprise a light chain that is at least 50% homologous to a sequence selected from SEQ ID NO. 30, SEQ ID NO. 31, SEQ ID NO. 36 and SEQ ID NO. 37. The chimeric antigen receptor-effector cell switch may comprise a light chain that is at least 60% homologous to a sequence selected from SEQ ID NO. 30, SEQ ID NO. 31, SEQ ID NO. 36 and SEQ ID NO. 37. The chimeric antigen receptor-effector cell switch may comprise a light chain that is at least 70% homologous to a sequence selected from SEQ ID NO. 30, SEQ ID NO. 31, SEQ ID NO. 36 and SEQ ID NO. 37. The chimeric antigen receptor-effector cell switch may comprise a light chain that is at least 80% homologous to a sequence selected from SEQ ID NO. 30, SEQ ID NO. 31, SEQ ID NO. 36 and SEQ ID NO. 37. The chimeric antigen receptor-effector cell switch may comprise a light chain that is at least 90% homologous to a sequence selected from SEQ ID NO. 30, SEQ ID NO. 31, SEQ ID NO. 36 and SEQ ID NO. 37.

[0077] The chimeric antigen receptor-effector cell switch may comprise a heavy chain of SEQ ID NO. 29 and a light chain of SEQ ID NO. 30. The chimeric antigen receptor-effector cell switch may comprise a heavy chain of SEQ ID NO. 29 and a light chain of SEQ ID NO. 36. The chimeric antigen receptor-effector cell switch may comprise a heavy chain of SEQ ID NO. 28 and a light chain of SEQ ID NO. 31. The chimeric antigen receptor-effector cell switch may comprise a heavy chain of SEQ ID NO. 32 and a light chain of SEQ ID NO. 27. The chimeric antigen receptor-effector cell switch may comprise a heavy chain of SEQ ID NO. 33 and a light chain of SEQ ID NO. 27. The chimeric antigen receptor-effector cell switch may comprise a heavy chain of SEQ ID NO. 34 and a light chain of SEQ ID NO. 27. The chimeric antigen receptor-effector cell switch may comprise a heavy chain of SEQ ID NO. 35 and a light chain of SEQ ID NO. 27. The chimeric antigen receptor-effector cell switch may comprise a heavy chain of SEQ ID NO. 38 and a light chain of SEQ ID NO. 37.

Multivalent CAR -EC Switches

[0078] Exemplified herein are CAR-EC switches comprising a chimeric antigen receptor binding peptidic antigen (CAR-BP) and a targeting polypeptide. However, one skilled in the art would understand that these switches could further comprise additional targeting polypeptides and/or additional CAR-BPs. One or more CAR-BPs may be grafted into one or more grafting sites of the targeting polypeptide. One or more CAR-BPs may be fused to one or more termini of the targeting polypeptide. This may be advantageous, as several grafting/fusing sites may be predicted to provide optimal binding of the CAR-BP to the CAR. For example, a first CAR-BP may be grafted into a first domain of the targeting polypeptide and a second CAR-BP may be grafted into a second domain of the targeting polypeptide. The first domain and the second domain may be the same. The first domain and the second domain may be different. By way of non-limiting example, the first CAR-BP may be grafted into a light chain of a targeting antibody or antibody fragment and a second CAR-BP may be grafted into heavy chain of the targeting antibody or antibody fragment. The first CAR-BP may be fused to a first terminus of the targeting polypeptide and a second CAR-BP may be fused to a second terminus of the targeting polypeptide. By way of non-limiting example, the first CAR-BP may be fused to a C terminus of a light chain of a targeting antibody or antibody fragment and a second CAR-BP may be fused to an N terminus of a heavy chain of the targeting antibody or antibody fragment. The first CAR-BP may be fused to a terminus of the targeting polypeptide and a second CAR-BP may be grafted within a domain of the targeting polypeptide. The first CAR-BP and the second CAR-BP may be the same or similar, such that the CAR-EC switch may be used with a CAR-EC cell that expresses one CAR. The first CAR-BP and the second CAR-BP may be different, such that the CAR-EC switch may be used with a CAR-EC cell that expresses one or more CARs or multiple CAR-EC cells that express different CARs.

[0079] The peptide switches disclosed herein may comprise one or more CAR-BPs. The peptide switches disclosed herein may comprise two or more CAR-BPs. The peptide switches disclosed herein may comprise three or more CAR-BPs. The peptide switches disclosed herein may comprise 1, 2, 3, 4, 5, 6, 7 or more CAR-BPs. The one or more CAR-BPs may be fused or grafted to the targeting polypeptide via one or more linkers. Thus, the peptide switches disclosed herein may comprise one or more linkers (e.g., L1, L2). The peptide switches disclosed herein may comprise two or more linkers. The peptide switches disclosed herein may comprise three or more linkers. The peptide switches disclosed herein may comprise 1, 2, 3, 4, 5, 6, 7 or more linkers.

IB. Peptide-Small Molecule Switch

[0080] Further disclosed herein are CAR-EC switches comprising a CAR binding region and a targeting moiety, wherein the CAR binding region is a CAR-binding peptidic antigen and the targeting moiety is a non-peptidic small molecule. The non-peptidic small molecule may be a cell-targeting molecule, a chemical ligand, a nucleic acid, a vitamin, a substrate or a substrate analog. The non-peptidic small molecule may not comprise two amino acids, wherein the two amino acids are connected by an amide bond. The CAR-EC switch may further comprise a linker. The CAR-binding peptidic antigen (CAR-BP) and the small molecule may be site-specifically linked. The CAR-binding peptidic antigen may comprise an unnatural amino acid. The CAR-binding peptidic antigen and the small molecule may be site-specifically linked by the unnatural amino acid. The small molecule may bind a cell surface molecule on a target cell. The cell surface molecule may be selected from an antigen, a protein, a peptide, a lipid, a sterol, a glycolipid and a cell surface marker. The CAR-binding peptidic antigen may be selected from FLAG® tag, yeast transcription factor GCN4 and a hydrophilic target peptide (HTP). The small molecule may be 2-[3-(1,3-dicarboxypropyl)ureido]pentanedioic acid. The small molecule may be folate. The CAR-EC switch may further comprise a linker.

[0081] Disclosed herein are methods of producing CAR-EC switches comprising conjugating the CAR binding region to the targeting moiety, wherein the CAR-EC switches comprise a CAR binding region and a targeting moiety, wherein the CAR binding region is a CAR-binding peptidic antigen and the targeting moiety is a small molecule. The method may further comprise conjugating the small molecule to the linker to create a small molecule-linker intermediate. The small molecule or the small molecule-linker intermediate may comprise one or more reactive functional groups that may react with a complementary reactive functional group on the CAR-BP, previous to incorporation into the CAR-EC switch. The linker or the small molecule-linker intermediate may be bifunctional. The linker or the small molecule-linker intermediate may be heterobifunctional.

[0082] The small molecule-linker intermediate or the CAR-EC switch may be the product of a bioorthogonal reaction, non-limiting examples of which are reviewed in Kim et al., Curr Opin Chem Bio 17:412-419 (2013). The small molecule-linker intermediate, linker or the CAR-EC switch may comprise an oxime, a tetrazole, a Diels Alder adduct, a hetero Diels Alder adduct, an aromatic substitution reaction product, a nucleophilic substitution reaction product, an ester, an amide, a carbamate, an ether, a thioether, or a Michael reaction product. The small molecule-linker intermediate, linker or the CAR-EC switch be a cycloaddition product, a metathesis reaction product, a metal-mediated cross-coupling reaction product, a radical polymerization product, an oxidative coupling product, an acyl-transfer reaction product, or a photo click reaction product. The cycloaddition may be a Huisgen-cycloaddition. The cycloaddition may be a copper-free [3+2] Huisgen-cycloaddition. The cycloaddition may be a Diels-Alder reaction. The cycloaddition may be a hetero Diels-Alder reaction. The small molecule-linker intermediate may be the product of an enzyme-mediated reaction. The small molecule-linker intermediate may be a product of a transglutaminase-mediated reaction, non-limiting examples of which are described in Lin et al., J. Am. Chem. Soc. 128:4542-4543 (2006) and WO 2013/093809. The small molecule-linker intermediate, linker or the CAR-EC switch may comprise a disulfide bridge that connects two cysteine residues, such as ThioBridge® technology by PolyTherics. The small molecule-linker intermediate, linker or the CAR-EC switch may comprise a maleimide bridge that connects two amino acid residues. The small molecule-linker inter-

mediate, linker or the CAR-EC switch may comprise a maleimide bridge that connects two cysteine residues.

[0083] The small molecule-linker intermediate or linker may comprise an alkoxy-amine (or aminooxy) group, azide group and/or cyclooctyne group at one or more termini. The small molecule-linker intermediate or linker may comprise an alkoxy-amine at one terminus and an azide group at the other terminus. The small molecule-linker intermediate or linker may comprise an alkoxy-amine at one terminus and a cyclooctyne group at the other terminus. The alkoxy-amine may form a stable oxime with a ketone group on an amino acid. The alkoxy-amine may form a stable oxime with a ketone group on an unnatural amino acid. The ketone group may be on a p-acetyl phenylalanine (pAcF).

II. Chimeric Antigen Receptor (CAR)

[0084] Disclosed herein are CAR-EC switches that regulate the activities of a cell expressing a chimeric antigen receptor (CAR). The chimeric antigen receptor may comprise an extracellular domain, transmembrane domain and intracellular domain. The extracellular domain may bind to the peptidic antigen (e.g. CAR-BP) of the CAR-EC switch. The extracellular domain may comprise an antibody or antibody fragment that binds to the CAR-BP of the CAR-EC switch (a CAR-antibody). The CAR-antibody may comprise at least a portion of an antibody. In some instances, the CAR-antibody is not a full-length antibody. The CAR-antibody may comprise at least a portion of an immunoglobulin or fragment thereof. The immunoglobulin or fragment thereof may be selected from the group consisting of an scFv, a di-scFv, a bi-scFv, a Fab, an Fc, an $F(ab')_2$, a pFc', a nanobody, an affibody, a DARPin, a diabody, a camelid, an engineered T cell receptor and a monobody. The immunoglobulin may be selected from the group consisting of an IgA1, an IgA2, an IgD, an IgM, an IgE, an IgG1, an IgG2, an IgG3, and an IgG4. The CAR-antibody may comprise at least a portion of a single chain variable fragment (scFv). The CAR-antibody may be human, fully human, humanized, human engineered, non-human, and/or chimeric antibody.

[0085] The CAR-antibody may have a binding affinity for the CAR-BP of less than about 0.01 pM, about 0.02 pM, about 0.03 pM, about 0.04 pM, 0.05 pM, about 0.06 pM, about 0.07 pM, about 0.08 pM, about 0.09 pM, about 0.1 pM, about 0.2 pM, 0.3 pM, about 0.4 pM, about 0.5 pM, about 0.6 pM, about 0.7 pM, about 0.8 pM, about 0.9 pM or about 1 pM, about 2 pM, about 3 pM, about 4 pM, about 5 pM, about 6 pM, about 7 pM, about 8 pM, about 9 pM, about 10 pM, about 0.01 nM, about 0.02 nM, about 0.03 nM, about 0.04 nM, about 0.05 nM, about 0.06 nM, about 0.07 nM, about 0.08 nM, about 0.09 nM, about 0.1 nM, about 0.2 nM, about 0.3 nM, about 0.4 nM, about 0.5 nM, about 0.6 nM, about 0.7 nM, about 0.8 nM, about 0.9 nM, about 1 nM, about 2 nM, about 2.5 nM, about 3 nM, about 4 nM, about 5 nM, about 6 nM, about 7 nM, about 8 nM, about 9 nM, about 10 nM, about 12 nM, about 14 nM, about 16 nM, about 18 nM, about 20 nM, about 22 nM, about 24 nM, about 26 nM, about 28 nM or about 30 nM.

[0086] The CAR-antibody may recognize a synthetic (non-naturally-occurring) peptide. The CAR-antibody may comprise an antibody or antibody fragment that recognizes a FLAG® tag or a fragment thereof. The CAR-antibody may comprise an antibody or antibody fragment that recognizes a yeast transcription factor GCN4 or a fragment thereof. The CAR-antibody may comprise an anti-HTP antibody or a fragment thereof.

[0087] The transmembrane domain and/or the intracellular domain of the CAR may comprise at least a portion of a cytoplasmic signaling domain. The intracellular domain may comprise at least a portion of a signaling molecule selected from the group comprising CD3zeta, CD28, and 4-1BB. The intracellular domain may comprise an Fc receptor or a portion thereof. The Fc receptor or portion thereof may be CD16 or a portion thereof. The signaling molecule may comprise CD3zeta. The signaling molecule may comprise CD28. The signaling molecule may comprise 4-1BB. The intracellular domain may comprise at least a portion of CD3zeta. The intracellular domain may comprise at least a portion of CD28, The intracellular domain may comprise at least a portion of 4-1BB, The intracellular domain may comprise at least a portion of OX-40, The intracellular domain may comprise at least a portion of CD30, The intracellular domain may comprise at least a portion of CD40, The intracellular domain may comprise at least a portion of CD2. The intracellular domain may comprise at least a portion of CD27. The intracellular domain may comprise at least a portion of PD-1. The intracellular domain may comprise at least a portion of ICOS. The intracellular domain may comprise at least a portion of lymphocyte function-associated antigen-1 (LFA-1). The intracellular domain may comprise at least a portion of CD7. The intracellular domain may comprise at least a portion of LIGHT. The intracellular domain may comprise at least a portion of NKG2C. The intracellular domain may comprise at least a portion of B7-H3. The intracellular domain may comprise at least a portion of a cytoplasmic signaling domain from one or more signaling molecules. The intracellular domain may comprise at least a portion of two or more cytoplasmic signaling domains. The two or more cytoplasmic signaling domains may be from two or more different signaling molecules. The intracellular domain may comprise at least a portion of three or more cytoplasmic signaling domains. The intracellular domain may comprise at least a portion of four or more cytoplasmic signaling domains. The intracellular domain may comprise at least a portion of a ligand that binds to one or more signaling molecules. The intracellular domain may comprise at least a portion of a ligand that binds to CD83.

III. Chimeric Antigen Receptor Effector Cells (CAR-EC)

[0088] The methods, platforms and kits disclosed herein may comprise one or more chimeric antigen receptor effector cells (CAR-EC) or uses thereof. The chimeric antigen receptor effector cells disclosed herein express a chimeric antigen receptor. The chimeric antigen receptor (CAR) may be any CAR disclosed herein. Wherein the methods, platforms or kits comprise two or more effector cells, the two or more effector cells may be of the same cell type. The two or more effector cells may be of a different cell type. The two or more effector cells may be of the same cell lineage. The two or more effector cells may be of different cell lineages. The two or more effector cells may comprise two or more identical CARs. The two or more effector cells may comprise two or more different CARs.

The two or more effector cells may comprise two or more similar CARs.

[0089] The effector cell may be a T cell. The effector cell may be a cell of a T cell lineage. The effector cell may be a mature T cell. The effector cell may be a precursor T cell. The effector cell may be a cytotoxic T cell. The effector cell may be a naive T cell. The effector cell may be a memory stem cell T cell (T_{MSC}). The effector cell may be a central memory T cell (T_{CM}). The effector cell may be an effector T cell (TE). The effector cell may be a CD4+ T cell. The T cell may be a CD8+ T cell. The effector cell may be a CD4+ and CD8+ cell. The effector cell may be an alpha-beta T cell. The effector cell may be a gamma-beta T cell. The effector cell may be a natural killer T cell. The effector cell may be a helper T cell.

[0090] While preferred embodiments of the present disclosure describe methods, kits and platforms comprising T cells, one skilled in the art may also understand that other cell types may be used in place of a T cell. The effector cell may be an effector cell that has an effect on a target or target cell when brought into proximity of the target or target cell. The effector cell may be a cell that has a cytotoxic effect on a target or target cell when brought into proximity of the target or target cell. The effector cell may be an immune cell. The effector cell may be selected from a B cell, a monocyte, a thrombocyte, a leukocyte, a neutrophil, an eosinophil, a basophil, or a lymphocyte. The effector cell may be a lymphocyte. The effector cell may be a macrophage. The effector cell may be a phagocytic cell. The effector cell may be an effector B cell. The effector cell may be a natural killer cell. The effector cell may isolated or derived from a subject suffering from a disease or condition. The effector cell may be a cell derived from a subject to be treated with a CAR-EC switch or CAR-EC platform disclosed herein.

[0091] The T cell may express a chimeric antigen receptor encoded by one or more polynucleotides based on or derived from SEQ ID NO: 1. The polynucleotide may be at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95% identical to one or more polynucleotides based on or derived from SEQ ID NO: 1. The polynucleotide may be at least about 70% identical to one or more polynucleotides based on or derived from SEQ ID NO: 1. The polypeptide encoded by one or more polynucleotides may be based on or derived from SEQ ID NO: 1. The polypeptide may be encoded by a polynucleotide that is at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95% identical to one or more polynucleotides based on or derived from SEQ ID NO: 1. The polynucleotide may be constitutively expressed. The polynucleotide may be conditionally expressed.

[0092] Disclosed herein are methods of producing a chimeric antigen receptor effector cell (CAR-EC), the methods comprising introducing one or more polynucleotides encoding a chimeric antigen receptor or a chimeric antigen receptor complex into an effector cell. The effector cell may be a T cell. Introducing one or more polynucleotides encoding a chimeric antigen receptor or a chimeric antigen receptor complex into an effector cell may comprise transfecting the effector cell with the one or more polynucleotides. Introducing one or more polynucleotides encoding a chimeric antigen receptor or a chimeric antigen receptor complex into an effector cell may comprise virally infecting the effector cell with one or more viruses comprising the one or more polynucleotides encoding a chimeric antigen receptor disclosed herein. The virus may be a lentivirus. The virus may be an adenovirus. The virus may be a retrovirus. The virus may be an adeno-associated virus. The virus may be a self-complementary adeno-associated virus (scAAV). The virus may be a modified human immunodeficiency (HIV) virus. The virus may be a modified herpes simplex virus (HSV) virus. Other methods of producing the CAR-EC may comprise a method of transferring one or more polynucleotides encoding a chimeric antigen receptor into a cell, wherein the methods comprise adding a transposon, a zinc finger nuclease, a TALEN or a CRISPR to the cell. The transposon may be a sleeping beauty transposon. The one or more polynucleotides may be based on or derived from SEQ ID NO: 1.

IV. CAR-EC Platform

[0093] Disclosed herein are chimeric antigen receptor effector cell (CAR-EC) platforms comprising a an effector cell, wherein the effector cell comprises a polynucleotide encoding a chimeric antigen receptor (CAR); and a chimeric antigen receptor effector cell (CAR-EC) switch, wherein the CAR-EC switch comprises a CAR binding peptidic antigen and a targeting polypeptide and wherein the CAR-EC switch binds a cell surface molecule on a target cell. The CAR-EC switch may be selected from any CAR-EC switches disclosed herein.

[0094] The CAR-EC platforms may comprise two or more CAR-EC switches. The CAR-EC platforms may comprise 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more CAR-EC switches. The CAR-EC platforms may comprise may comprise more than 20, more than 25, more than 30, more than 35, more than 40, more than 45 or more than 50 CAR-EC switches. The two or more switches may be selected from one or more CAR-EC switches disclosed herein or a combination thereof.

[0095] The CAR-EC platforms disclosed herein may further comprise a first CAR-EC switch and a second CAR-EC switch, wherein the first CAR-EC switch comprises a first CAR-BP and a first targeting polypeptide and the second CAR-EC switch comprises a second CAR-BP and a second targeting polypeptide. The first CAR-BP and the second CAR-BP may be the same. The first CAR-BP and the second CAR-BP may be different. The first CAR-BP and the second CAR-BP may be about 99%, about 98%, about 97%, about 96%, about 95%, about 92%, about 90%, about 85%, about 80%, about 75%, about 70%, about 65%, about 60%, about 55%, about 50%, about 45%, about 40%, about 35%, about 30%, about 25%, about 20%, about 15%, about 10%, about 5% or about 2% homologous. The first targeting polypeptide and the second targeting polypeptide may be the same. The first targeting polypeptide and the second targeting polypeptide may be different. The first targeting polypeptide and the second targeting polypeptide may be about 99%, about 98%, about 97%, about 96%, about 95%, about 92%, about 90%, about 85%, about 80%, about 75%, about 70%, about 65%, about 60%, about 55%, about 50%, about 45%, about 40%, about 35%, about 30%, about 25%, about 20%, about 15%, about 10%, about 5% or about 2% homologous.

V. Kits, Vectors and Polynucleotides

[0096] Disclosed herein are kits comprising one or more CAR-EC switches disclosed herein. The kit may further comprise two or more CAR-EC switches. The kit may comprise three CAR-EC switches. The kit may comprise about 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 20, 24, 30, 35, 48, 50, 55, 60, 65, 70, 75, 80, 85, 90, 96, 100, 120, 150, 200, 300, 384, 400, 500, 600, 700, 800, 900 or 1000 CAR-EC switches. The kit may be employed for biological research. The kit may be used for diagnosing a disease or a condition. The kit may be used for treating a disease or condition. The CAR-EC switches of the kit may be used with CAR-EC cells disclosed herein or existing CAR T-cells clinically used or tested. The kit may further comprise one or more effector cells. The kit may further comprise one or more CAR-EC cells. The CAR-EC cell may be a T cell. The T cell may express one or more CARs. The kit may further comprise a polynucleotide encoding one or more CARs. The kit may further comprise a vector comprising a polynucleotide encoding one or more CARs. The CAR may be selected from any of the CARs disclosed herein. The kit may comprise one or more polynucleotide encoding a CAR-EC switch disclosed herein or a portion thereof (e.g. antibody, antibody fragment, peptide).

[0097] Further disclosed herein are and vectors and polynucleotides encoding CAR-EC switches or portions thereof, wherein the CAR-EC switch comprises a chimeric antigen receptor binding peptidic antigen and a targeting polypeptide, wherein the targeting peptide binds a cell surface molecule on a target cell. The polynucleotides may be DNA. The polynucleotides may be RNA. Unless otherwise specified, the terms "polynucleotide" and "vector," as used herein, are used interchangeably. The targeting polypeptide may be an antibody or antibody fragment. The vector may comprise a sequence encoding a heavy chain of the antibody or antibody fragment. The vectors may comprise a sequence encoding a light chain of the antibody or antibody fragment. The vectors may comprise the sequence encoding the light chain of the antibody or antibody fragment and the sequence encoding the heavy chain of the antibody or antibody fragment. The light chain and the heavy chain may be expressed from the same vector. The light chain and the heavy chain may be expressed from two separate vectors.

[0098] Disclosed herein are vectors and polynucleotides encoding chimeric antigen receptors, wherein the chimeric antigen receptors comprise an extracellular domain that binds to a peptide of a chimeric antigen receptor effector cell switch. The extracellular domain may comprise an antibody or antibody fragment. The antibody or antibody fragment may bind a peptidic antigen of a chimeric antigen receptor effector cell switch . The peptidic antigen may be a yeast peptide. The yeast peptide may be GCN4. f a or portions thereof may be encoded by one or more polynucleotides based on or derived from SEQ ID NO: 1. CARs or portions thereof may be encoded by a polynucleotide at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95% identical to one or more polynucleotides based on or derived from SEQ ID NO: 1. CARs or portions thereof encoded by a polynucleotide may be at least about 70% identical to one or more polynucleotides based on or derived from SEQ ID NO: 1. Disclosed herein are vectors comprising one or more polynucleotides based on or derived from SEQ ID NO: 1.

[0099] Vectors comprising sequences encoding chimeric antigen receptors and/or chimeric antigen receptor effector cell switches and portions thereof, disclosed herein, may be selected from any commercially available expression vector. The expression vector may be a prokaryotic expression vector. The expression vector may be a eukaryotic expression vector. The expression vector may be a mammalian expression vector. The expression vector may be a viral expression vector. The expression vector may have a constitutive promoter for constitutive expression of the CAR and/or CAR-EC switch encoding sequences. The expression vector may have an inducible promoter for conditional expression of the CAR and/or CAR-EC switch encoding sequences.

VI. Therapeutic Use

[0100] Disclosed herein are methods, platforms and kits for treating a disease or condition in a subject in need thereof, the method comprising administering a chimeric antigen receptor effector cell (CAR-EC) switch to the subject, wherein the CAR-EC switch comprises: a CAR-binding peptidic antigen; and a targeting moiety. Disclosed herein are methods of treating a disease or condition in a subject in need thereof, the method comprising administering any one of the CAR-EC switches disclosed herein.

[0101] The methods may comprise administering a CAR-EC cell and one or more CAR-EC switches. The methods may comprise administering about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 20, 24, 30, 35, 48, 50, 55, 60, 65, 70, 75, 80, 85, 90, 96, 100, 120, 150, 200, 300, 384, 400, 500, 600, 700, 800, 900, 1000 or more CAR-EC switches. The methods may comprise administering two or more CAR-EC switches. The two or more CAR-EC switches may comprise the same CAR-binding peptidic antigen. The two more CAR-EC switches may comprise the same cell targeting polypeptide. The two or more CAR-EC switches may comprise one or more different CAR-binding peptidic antigens. The two more CAR-EC switches may comprise one or more different cell targeting polypeptides. The methods may comprising a plurality of CAR-EC cells and one or more CAR-EC switches.

[0102] Disclosed herein are methods of treating a disease or condition in a subject in need thereof, the method comprising administering a chimeric antigen receptor effector cell (CAR-EC) switch to the subject, wherein the CAR-EC switch comprises: a chimeric antigen receptor binding peptidic antigen (CAR-BP); and a targeting moiety that binds an antigen on a target. The CAR-BP, by non-limiting example, may be selected from a FLAG® tag, a yeast transcription factor GCN4 and a hydrophilic target peptide (HTP). The targeting moiety, by non-limiting example may be selected from an anti-CD19 antibody, an anti-CD20 antibody, an anti-CD22 antibody, an anti-EGFR antibody, an anti-EGFR-vIII antibody, an anti-Her2 antibody, an anti-CS1 antibody, an anti-BCMA antibody, an anti-CEA antibody, an anti-CLL-1 antibody and an anti-CD33 antibody.

[0103] The methods may comprise administering one or more chimeric antigen receptor effector cells. The methods may comprise administering one or more T cells. The one or more effector cells may be selected from T cell is selected from a naive T cell, a memory stem cell T cell, a central memory T cell, an effector memory T cell, a helper T cell,

a CD4+ T cell, a CD8+ T cell, a CD8/CD4+ T cell, an αβ T cell, a γδ T cell, a cytotoxic T cell, a natural killer T cell, a natural killer cell, a macrophage.

[0104] The CAR-EC switch may have a therapeutic effect that is at least partially dependent on bringing an effector cell in proximity of a target cell. The therapeutic effect on the intended indication of the CAR-EC switch may be at least partially due to the CAR-EC switch recruiting an effector cell to the target cell. The therapeutic effect on the intended indication of the CAR-EC switch may be predominantly due to the CAR-EC switch recruiting an effector cell to the target cell. The therapeutic effect of the CAR-EC switch may be at least partially dependent on stimulating an immune response in the CAR-EC cell.

[0105] Administering the CAR-EC switch may not have any therapeutic effect without further administering an effector cell. The CAR-EC switch may not have a significant, desirable and/or intended therapeutic effect without further administering an effector cell. The CAR-EC switch may not have any therapeutic effect towards an intended indication of the CAR-EC platform without further administering an effector cell. A portion or component of the CAR-EC switch (e.g. CAR-BP or targeting moiety) may not have a therapeutic effect towards the intended indication of the CAR-EC switch without being conjugated to a second portion or component of the CAR-EC switch (e.g. CAR-BP or targeting moiety). The dose of a portion or component of the CAR-EC switch (e.g. CAR-BP or targeting moiety) when administered as part of the CAR-EC platform to provide a therapeutic effect may not have a therapeutic effect when the portion or component of the CAR-EC switch is administered alone at that dose. The portion or component of the CAR-EC switch may not be intended to have any therapeutic effect besides recruiting the T cell to the target cell. Administering the portion or component of the CAR-EC switch alone may have a therapeutic effect on the target cell, wherein the therapeutic effect is negligible relative to the therapeutic effect of administering the CAR-EC switch and the CAR-EC cell. Administering the portion or component of the CAR-EC switch may have a therapeutic effect on the target cell, wherein the therapeutic effect is less than the therapeutic effect of administering the CAR-EC switch and the CAR-EC cell.

[0106] Disclosed herein are uses of CAR-EC switches disclosed herein to treat a disease or condition in a subject in need thereof. Further disclosed herein are uses of CAR-EC switches disclosed herein in the manufacture of a medicament for the treatment of a disease.

[0107] Disclosed herein is use of a switch comprising a peptidic antigen that binds a CAR (CAR-BP) on an effector cell; and a targeting polypeptide that binds an antigen on a target to treat a disease or condition in a subject in need thereof. Further disclosed herein is use of a switch comprising a peptidic antigen (CAR-BP) that binds a CAR on an effector cell, wherein the CAR-BP; and a targeting polypeptide that binds an antigen on a target in the manufacture of a medicament for the treatment of a disease.

[0108] Disclosed herein is use of a CAR-EC switch comprising a CAR-BP, wherein the CAR-BP comprises a hydrophilic target peptide (HTP) or derivative thereof and a targeting polypeptide, wherein the targeting polypeptide comprises an anti-CD19 antibody or fragment thereof; and an effector cell comprising a CAR, wherein the CAR comprises an anti-HTP antibody, wherein the anti-CD19 antibody or fragment thereof binds CD19 on a B cell to treat a multiple myeloma.

[0109] Disclosed herein is use of a CAR-EC switch comprising a CAR-BP, wherein the CAR-BP comprises a yeast transcription factor GCN4 or derivative thereof and a targeting polypeptide, wherein the targeting polypeptide comprises an anti-CD19 antibody or fragment thereof; and an effector cell comprising a CAR, wherein the CAR comprises an anti-GCN4 antibody, wherein the anti-CD19 antibody or fragment thereof binds CD19 on a lymphoblast, lymphocyte or B cell, to treat an acute lymphoblastic leukemia, a chronic lymphocytic leukemia or a B-cell lymphoma.

[0110] The disease or condition may be a cell proliferative disorder. The cell proliferative disorder may be selected from a solid tumor, a lymphoma, a leukemia and a liposarcoma. The cell proliferative disorder may be acute, chronic, recurrent, refractory, accelerated, in remission, stage I, stage II, stage III, stage IV, juvenile or adult. The cell proliferative disorder may be selected from myelogenous leukemia, lymphoblastic leukemia, myeloid leukemia, an acute myeloid leukemia, myelomonocytic leukemia, neutrophilic leukemia, myelodysplastic syndrome, B-cell lymphoma, burkitt lymphoma, large cell lymphoma, mixed cell lymphoma, follicular lymphoma, mantle cell lymphoma, hodgkin lymphoma, recurrent small lymphocytic lymphoma, hairy cell leukemia, multiple myeloma, basophilic leukemia, eosinophilic leukemia, megakaryoblastic leukemia, monoblastic leukemia, monocytic leukemia, erythroleukemia, erythroid leukemia and hepatocellular carcinoma. The cell proliferative disorder may comprise a hematological malignancy. The hematological malignancy may comprise a B cell malignancy. The cell proliferative disorder may comprise a chronic lymphocytic leukemia. The cell proliferative disorder may comprise an acute lymphoblastic leukemia. The cell proliferative disorder may comprise a CD19-positive Burkitt's lymphoma.

[0111] The disease or condition may be a cancer, a pathogenic infection, autoimmune disease, inflammatory disease, or genetic disorder.

[0112] In some instances, the one or more diseases comprises a cancer. The cancer may comprise a recurrent and/or refractory cancer. Examples of cancers include, but are not limited to, sarcomas, carcinomas, lymphomas or leukemias.

[0113] The cancer may comprise a neuroendocrine cancer. The cancer may comprise a pancreatic cancer. The cancer may comprise an exocrine pancreatic cancer. The cancer may comprise a thyroid cancer. The thyroid cancer may comprise a medullary thyroid cancer. The cancer may comprise a prostate cancer.

[0114] The cancer may comprise an epithelial cancer. The cancer may comprise a breast cancer. The cancer may comprise an endometrial cancer. The cancer may comprise an ovarian cancer. The ovarian cancer may comprise a stromal ovarian cancer. The cancer may comprise a cervical cancer.

[0115] The cancer may comprise a skin cancer. The skin cancer may comprise a neo-angiogenic skin cancer. The skin cancer may comprise a melanoma.

[0116] The cancer may comprise a kidney cancer.

[0117] The cancer may comprise a lung cancer. The lung cancer may comprise a small cell lung cancer. The lung cancer may comprise a non-small cell lung cancer.

[0118] The cancer may comprise a colorectal cancer. The cancer may comprise a gastric cancer. The cancer may comprise a colon cancer.

[0119] The cancer may comprise a brain cancer. The brain cancer may comprise a brain tumor. The cancer may comprise a glioblastoma. The cancer may comprise an astrocytoma.

[0120] The cancer may comprise a blood cancer. The blood cancer may comprise a leukemia. The leukemia may comprise a myeloid leukemia. The cancer may comprise a lymphoma. The lymphoma may comprise a non-Hodgkin's lymphoma.

[0121] The cancer may comprise a sarcoma. The sarcoma may comprise an Ewing's sarcoma.

[0122] Sarcomas are cancers of the bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue. Sarcomas include, but are not limited to, bone cancer, fibrosarcoma, chondrosarcoma, Ewing's sarcoma, malignant hemangioendothelioma, malignant schwannoma, bilateral vestibular schwannoma, osteosarcoma, soft tissue sarcomas (e.g. alveolar soft part sarcoma, angiosarcoma, cystosarcoma phylloides, dermatofibrosarcoma, desmoid tumor, epithelioid sarcoma, extraskeletal osteosarcoma, fibrosarcoma, hemangiopericytoma, hemangiosarcoma, Kaposi's sarcoma, leiomyosarcoma, liposarcoma, lymphangiosarcoma, lymphosarcoma, malignant fibrous histiocytoma, neurofibrosarcoma, rhabdomyosarcoma, and synovial sarcoma).

[0123] Carcinomas are cancers that begin in the epithelial cells, which are cells that cover the surface of the body, produce hormones, and make up glands. By way of non-limiting example, carcinomas include breast cancer, pancreatic cancer, lung cancer, colon cancer, colorectal cancer, rectal cancer, kidney cancer, bladder cancer, stomach cancer, prostate cancer, liver cancer, ovarian cancer, brain cancer, vaginal cancer, vulvar cancer, uterine cancer, oral cancer, penile cancer, testicular cancer, esophageal cancer, skin cancer, cancer of the fallopian tubes, head and neck cancer, gastrointestinal stromal cancer, adenocarcinoma, cutaneous or intraocular melanoma, cancer of the anal region, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, cancer of the urethra, cancer of the renal pelvis, cancer of the ureter, cancer of the endometrium, cancer of the cervix, cancer of the pituitary gland, neoplasms of the central nervous system (CNS), primary CNS lymphoma, brain stem glioma, and spinal axis tumors. In some instances, the cancer is a skin cancer, such as a basal cell carcinoma, squamous, melanoma, nonmelanoma, or actinic (solar) keratosis.

[0124] In some instances, the cancer is a lung cancer. Lung cancer may start in the airways that branch off the trachea to supply the lungs (bronchi) or the small air sacs of the lung (the alveoli). Lung cancers include non-small cell lung carcinoma (NSCLC), small cell lung carcinoma, and mesotheliomia. Examples of NSCLC include squamous cell carcinoma, adenocarcinoma, and large cell carcinoma. The mesothelioma may be a cancerous tumor of the lining of the lung and chest cavity (pleura) or lining of the abdomen (peritoneum). The mesothelioma may be due to asbestos exposure. The cancer may be a brain cancer, such as a glioblastoma.

[0125] Alternatively, the cancer may be a central nervous system (CNS) tumor. CNS tumors may be classified as gliomas or nongliomas. The glioma may be malignant glioma, high grade glioma, diffuse intrinsic pontine glioma. Examples of gliomas include astrocytomas, oligodendrogliomas (or mixtures of oligodendroglioma and astocytoma elements), and ependymomas. Astrocytomas include, but are not limited to, low-grade astrocytomas, anaplastic astrocytomas, glioblastoma multiforme, pilocytic astrocytoma, pleomorphic xanthoastrocytoma, and subependymal giant cell astrocytoma. Oligodendrogliomas include low-grade oligodendrogliomas (or oligoastrocytomas) and anaplastic oligodendriogliomas. Nongliomas include meningiomas, pituitary adenomas, primary CNS lymphomas, and medulloblastomas. In some instances, the cancer is a meningioma.

[0126] The leukemia may be an acute lymphocytic leukemia, acute myelocytic leukemia, chronic lymphocytic leukemia, or chronic myelocytic leukemia. Additional types of leukemias include hairy cell leukemia, chronic myelomonocytic leukemia, and juvenile myelomonocytic leukemia.

[0127] Lymphomas are cancers of the lymphocytes and may develop from either B or T lymphocytes. The two major types of lymphoma are Hodgkin's lymphoma, previously known as Hodgkin's disease, and non-Hodgkin's lymphoma. Hodgkin's lymphoma is marked by the presence of the Reed-Sternberg cell. Non-Hodgkin's lymphomas are all lymphomas which are not Hodgkin's lymphoma. Non-Hodgkin lymphomas may be indolent lymphomas and aggressive lymphomas. Non-Hodgkin's lymphomas include, but are not limited to, diffuse large B cell lymphoma, follicular lymphoma, mucosa-associated lymphatic tissue lymphoma (MALT), small cell lymphocytic lymphoma, mantle cell lymphoma, Burkitt's lymphoma, mediastinal large B cell lymphoma, Waldenström macroglobulinemia, nodal marginal zone B cell lymphoma (NMZL), splenic marginal zone lymphoma (SMZL), extranodal marginal zone B cell lymphoma, intravascular large B cell lymphoma, primary effusion lymphoma, and lymphomatoid granulomatosis.

[0128] The cancer may comprise a solid tumor. The cancer may comprise a sarcoma. The cancer may be selected from a group consisting of a bladder cancer, a breast cancer, a colon cancer, a rectal cancer, an endometrial cancer, a kidney cancer, a lung cancer, melanoma, a myeloma, a thyroid cancer, a pancreatic cancer, a glioma, a malignant glioma of the brain, a glioblastoma, an ovarian cancer, and a prostate cancer. The cancer may have non-uniform antigen expression. The cancer may have modulated antigen expression. The antigen may be a surface antigen. The cancer may not comprise a myeloma. The cancer may not comprise a melanoma. The cancer may not comprise a colon cancer. The cancer may be acute lymphoblastic leukemia (ALL). The cancer may be relapsed ALL. The cancer may be refractory ALL. The cancer may be relapsed, refractory ALL. The cancer may be chronic lymphocytic leukemia (CLL). The cancer may be relapsed CLL. The cancer may be refractory CLL. The cancer may be relapsed, refractory CLL.

[0129] The cancer may comprise a breast cancer. The breast cancer may be triple positive breast cancer (estrogen receptor, progesterone receptor and Her2 positive). The breast cancer may be triple negative breast cancer (estrogen receptor, progesterone receptor and Her2 negative). The breast cancer may be estrogen receptor positive. The breast cancer may be estrogen receptor negative. The breast cancer may be progesterone receptor positive. The breast cancer may be progesterone receptor negative. The breast cancer may comprise a Her2 negative breast cancer. The breast cancer may comprise a low-expressing Her2 breast cancer. The breast cancer may comprise a Her2 positive breast cancer.

Cell lines expressing Her2 have been well-characterized for antigen density, reflecting clinical immunohistochemistry characterization which classifies malignancies as 0 (<20,000 Her2 antigens per cell), 1+ (100,000 Her2 antigens per cell), 2+ (500,000 Her2 antigens per cell), and 3+ (>2,000,000 Her2 antigens per cell). The present invention provides for methods of treating breast cancers of these classifications. The breast cancer may comprise a breast cancer classified as Her2 0. The breast cancer may comprise a breast cancer classified as Her2 1+. The breast cancer may comprise a breast cancer classified as Her2 2+. The breast cancer may comprise a breast cancer classified as a Her2 3+.

[0130] The disease or condition may be a pathogenic infection. Pathogenic infections may be caused by one or more pathogens. In some instances, the pathogen is a bacterium, fungi, virus, or protozoan.

[0131] Exemplary pathogens include but are not limited to: *Bordetella, Borrelia, Brucella, Campylobacter, Chlamydia, Chlamydophila, Clostridium, Corynebacterium, Enterococcus, Escherichia, Francisella, Haemophilus, Helicobacter, Legionella, Leptospira, Listeria, Mycobacterium, Mycoplasma, Neisseria, Pseudomonas, Rickettsia, Salmonella, Shigella, Staphylococcus, Streptococcus, Treponema, Vibrio*, or *Yersinia*. In some cases, the disease or condition caused by the pathogen is tuberculosis and the heterogeneous sample comprises foreign molecules derived from the bacterium *Mycobacterium tuberculosis* and molecules derived from the subject. In some instances, the disease or condition is caused by a bacterium is tuberculosis, pneumonia, which may be caused by bacteria such as *Streptococcus* and *Pseudomonas*, a foodborne illness, which may be caused by bacteria such as *Shigella, Campylobacter* and *Salmonella*, and an infection such as tetanus, typhoid fever, diphtheria, syphilis and leprosy. The disease or condition may be bacterial vaginosis, a disease of the vagina caused by an imbalance of naturally occurring bacterial flora. Alternatively, the disease or condition is a bacterial meningitis, a bacterial inflammation of the meninges (e.g., the protective membranes covering the brain and spinal cord). Other diseases or conditions caused by bacteria include, but are not limited to, bacterial pneumonia, a urinary tract infection, bacterial gastroenteritis, and bacterial skin infection. Examples of bacterial skin infections include, but are not limited to, impetigo which may be caused by *Staphylococcus aureus* or *Streptococcus pyogenes*; erysipelas which may be caused by a *streptococcus* bacterial infection of the deep epidermis with lymphatic spread; and cellulitis which may be caused by normal skin flora or by exogenous bacteria.

[0132] The pathogen may be a fungus, such as, *Candida, Aspergillus, Cryptococcus, Histoplasma, Pneumocystis*, and *Stachybotrys*. Examples of diseases or conditions caused by a fungus include, but are not limited to, jock itch, yeast infection, ringworm, and athlete's foot.

[0133] The pathogen may be a virus. Examples of viruses include, but are not limited to, adenovirus, coxsackievirus, Epstein-Barr virus, Hepatitis virus (e.g., Hepatitis A, B, and C), herpes simplex virus (type 1 and 2), cytomegalovirus, herpes virus, HIV, influenza virus, measles virus, mumps virus, papillomavirus, parainfluenza virus, poliovirus, respiratory syncytial virus, rubella virus, and varicella-zoster virus. Examples of diseases or conditions caused by viruses include, but are not limited to, cold, flu, hepatitis, AIDS, chicken pox, rubella, mumps, measles, warts, and poliomyelitis.

[0134] The pathogen may be a protozoan, such as Acanthamoeba (e.g., *A. astronyxis, A. castellanii, A. culbertsoni, A. hatchetti, A. polyphaga, A. rhysodes, A. healyi, A. divionensis*), *Brachiola* (e.g., *B connori, B. vesicularum*), *Cryptosporidium* (e.g., *C. parvum*), *Cyclospora* (e.g., *C. cayetanensis*), *Encephalitozoon* (e.g., *E. cuniculi, E. hellem, E. intestinalis*), *Entamoeba* (e.g., *E. histolytica*), *Enterocytozoon* (e.g., *E. bieneusi*), *Giardia* (e.g., *G. lamblia*), *Isospora* (e.g, *I. belli*), *Microsporidium* (e.g., *M. africanum, M. ceylonensis*), *Naegleria* (e.g., *N. fowleri*), *Nosema* (e.g., *N. algerae, N. ocularum*), *Pleistophora, Trachipleistophora* (e.g., *T. anthropophthera, T. hominis*), and *Vittaforma* (e.g., *V. corneae*).

[0135] The disease or condition may be an autoimmune disease or autoimmune related disease. An autoimmune disorder may be a malfunction of the body's immune system that causes the body to attack its own tissues. Examples of autoimmune diseases and autoimmune related diseases include, but are not limited to, Addison's disease, alopecia areata, ankylosing spondylitis, antiphospholipid syndrome (APS), autoimmune aplastic anemia, autoimmune hemolytic anemia, autoimmune hepatitis, autoimmune myocarditis, Behcet's disease, celiac sprue, Crohn's disease, dermatomyositis, eosinophilic fasciitis, erythema nodosum, giant cell arteritis (temporal arteritis), Goodpasture's syndrome, Graves' disease, Hashimoto's disease, idiopathic thrombocytopenic purpura (ITP), IgA nephropathy, juvenile arthritis, diabetes, juvenile diabetes, Kawasaki syndrome, Lambert-Eaton syndrome, lupus (SLE), mixed connective tissue disease (MCTD), multiple sclerosis, myasthenia gravis, pemphigus, polyarteritis nodosa, type I, II, & III autoimmune polyglandular syndromes, polymyalgia rheumatica, polymyositis, psoriasis, psoriatic arthritis, Reiter's syndrome, relapsing polychondritis, rheumatoid arthritis, sarcoidosis, scleroderma, Sjogren's syndrome, sperm & testicular autoimmunity, stiff person syndrome, Takayasu's arteritis, temporal arteritis/giant cell arteritis, ulcerative colitis, uveitis, vasculitis, vitiligo, and Wegener's granulomatosis.

[0136] The disease or condition may be an inflammatory disease. Examples of inflammatory diseases include, but are not limited to, alveolitis, amyloidosis, angiitis, ankylosing spondylitis, avascular necrosis, Basedow's disease, Bell's palsy, bursitis, carpal tunnel syndrome, celiac disease, cholangitis, chondromalacia patella, chronic active hepatitis, chronic fatigue syndrome, Cogan's syndrome, congenital hip dysplasia, costochondritis, Crohn's Disease, cystic fibrosis, De Quervain's tendinitis, diabetes associated arthritis, diffuse idiopathic skeletal hyperostosis, discoid lupus, Ehlers-Danlos syndrome, familial mediterranean fever, fasciitis, fibrositis/fibromyalgia, frozen shoulder, ganglion cysts, giant cell arteritis, gout, Graves' Disease, HIV-associated rheumatic disease syndromes, hyperparathyroid associated arthritis, infectious arthritis, inflammatory bowel syndrome/ irritable bowel syndrome, juvenile rheumatoid arthritis, lyme disease, Marfan's Syndrome, Mikulicz's Disease, mixed connective tissue disease, multiple sclerosis, myofascial pain syndrome, osteoarthritis, osteomalacia, osteoporosis and corticosteroid-induced osteoporosis, Paget's Disease, palindromic rheumatism, Parkinson's Disease, Plummer's Disease, polymyalgia rheumatica, polymyositis, pseudogout, psoriatic arthritis, Raynaud's Phenomenon/Syndrome, Reiter's Syndrome, rheumatic fever, rheumatoid arthritis, sarcoidosis, sciatica (lumbar radiculo-

pathy), scleroderma, scurvy, sickle cell arthritis, Sjogren's Syndrome, spinal stenosis, spondyloisthesis, Still's Disease, systemic lupus erythematosis, Takayasu's (Pulseless) Disease, Tendinitis, tennis elbow/golf elbow, thyroid associated arthritis, trigger finger, ulcerative colitis, Wegener's Granulomatosis, and Whipple's Disease.

[0137] Methods of treatment disclosed herein may comprise off-target activity as measured by cytokine levels. The method may reduce the off-target activity, as measured by cytokine levels, when compared to other CAR-EC therapies. The method may reduce the off-target activity as measured by interferon gamma levels. Other off-target activities that may be reduced include toxic lymphophenia, fatal cytolysis of solid tumor targets and chronic hypogammaglobulinemia for hematological targets. Methods of treatment and compositions disclosed herein may be used to treat a cancer comprising CD19-mediated B cell aplasia. The methods and compositions may minimize the CD19-mediated B cell aplasia. The method may avoid long-term B-cell aplasia.

[0138] The CAR-EC platforms, methods and compositions disclosed herein may be used to treat a heterogeneous tumor or a heterogeneous blood cell malignancy in a subject in need thereof._The "pan-B cell" marker CD20 is the most prevalently targeted antigen for B cell neoplasms and the FDA-approved antibody rituximab is a vital component in the treatment of many leukemias and lymphomas. However, resistance mechanisms related to modulation of CD20 antigen expression occurs in a significant number of patients. It is clear that targeting with either CD19 or CD20 antigen alone is insufficient for a curative therapy. The methods disclosed herein provide for construction and administration of two or more switches with different specificities (e.g. an anti-CD19 antibody CAR-EC switch and an anti-CD20 antibody CAR-EC switch). The methods disclosed herein provide for construction and administration of two or more switches with different specificities (e.g. an anti-CD19 antibody CAR-EC switch and an anti-CD22 antibody CAR-EC switch). This methodology may offer a significant advantage against the propensity for relapse in the clinic while avoiding persistent loss of B cells. A heterogeneous tumor or heterogeneous blood cell malignancy may also be treated with an anti-CD19 antibody CAR-EC switch and an anti-CD22 antibody CAR-EC switch. One or more CAR-EC switches may be administered sequentially or simultaneously.

[0139] The CAR-EC switch may be administered with one or more additional therapeutic agents. The one or more additional therapeutic agents may be selected from a group consisting of an immunotherapy, a chemotherapy and a steroid. The one or more additional therapeutic agents may be a chemotherapy drug. The chemotherapy drug may be an alkylating agent, an antimetabolite, an anthracycline, a topoisomerase inhibitor, a mitotic inhibitor, a corticosteroid or a differentiating agent. The chemotherapy drug may be selected from actinomycin-D, bleomycin, altretamine, bortezomib, busulfan, carboplatin, capecitabine, carmustine, chlorambucil, cisplatin, cladribine, clofarabine, cyclophosphamide, cytarabine, dacarbazine, daunorubicin, docetaxel, doxorubicin, epirubicin, etoposide, estramustine, floxuridine, fludarabine, fluorouracil, gemcitbine (Gemzar), hydroxyurea, idarubicin, ifosfamide, irinotecan (Camptosar), ixabepilone, L-asparaginase, lomustine, mechlorethamine, melphalan, 6-mercaptopurine, methotrexate, mitomycin-C, paclitaxel (Taxol), pemetrexed, pentostatin, streptozocin, temozolomide, teniposide, thioguanine, thiotepa, topotecan (Hycamtin), vincristine, vinblastine, vinorelbine, retinoids, tretinoin (ATRA or Atralin®), bexarotene (Targretin®) and arsenic trioxide (Arsenox®). The chemotherapy may be administered as a pill to swallow, as an injection into the muscle or fat tissue, intravenously, topically or directly into a body cavity.

[0140] The one or more additional therapeutic agents may comprise an angiogenesis inhibitor. The angiogenesis inhibitor may be selected from bevacizumab, itraconazole, carboxyamidotriazole, TNP-470, CM101, IFN alpha, IL-12, platelet factor 4, suramin, SU5416, thrombospondin, a VEGFR antagonist, an angiostatic steroid with heparin, CAR-ECilage-derived angiogenesis inhibitory factor, matrix metalloprotease inhibitors, angiostatin, endostatin, sorafenib, sunitinib, pazopanib, everolimus, 2-methoxyestradiol, tecogalan, tetrathiomolybdate, thalidomide, prolactin, $\alpha v\beta_3$ inhibitor, linomide, tasquinimod, soluble VEGFR-1, soluble NRP-1, angiopoietin 2, vasostatin, calreticulin, TIMP, CDAI, Meth-1, Meth-2, interferon-alpha, interferon-beta, interferon-gamma, CXCL10, IL-4, IL-12, IL-18, prothrombin, antithrombin III fragment, prolactin, VEGI, SPARC, osteopontin, maspin, canstatin, proliferin-related protein and restin.

[0141] The one or more additional therapeutic agents may comprise a hormone therapy. The hormone therapy may be selected from an anti-estrogen (e.g. fulvestrant (Faslodex®), tamoxifen, toremifene (Fareston®)); an aromatase inhibitor (e.g. anastrozole (Arimidex®), exemestane (Aromasin®), letrozole (Femara®)); a progestin (e.g. megestrol acetate (Megace®)); an estrogen; an anti-androgen (e.g. bicalutamide (Casodex®), flutamide (Eulexin®), nilutamide (Nilandron®)); a gonadotropin-releasing hormone (GnRH) or luteinizing hormone-releasing hormone (LHRH) agonist or analog (e.g. leuprolide (Lupron®), goserelin (Zoladex®)).

[0142] The one or more additional therapeutic agents may comprise a steroid. The steroid may be a corticosteroid. The steroid may be cortisol or a derivative thereof. The steroid may be selected from prednisone, methylprednisolone (Solumedrol®) or dexamethasone.

[0143] The CAR-EC switch may be administered with one or more additional therapies. The one or more additional therapies may comprise laser therapy. The one or more additional therapies may comprise radiation therapy. The one or more additional therapies may comprise surgery.

[0144] Disclosed herein are platforms, kits and methods for treating a disease or condition in a subject. The subject may be a healthy subject. The subject may be suffering from a disease or condition. The subject may be suffering from more than one disease or condition. The subject may be suffering from chronic lymphocytic leukemia. The subject may be suffering from acute lymphoblastic leukemia. The subject may be an animal. The subject may be a mammal. The mammal may be a human, a chimpanzee, a gorilla, a monkey, a bovine, a horse, a donkey, a mule, a dog, a cat, a pig, a rabbit, a goat, a sheep, a rat, a hamster, a guinea pig or a mouse. The subject may be a bird or a chicken. The subject may be a human. The subject may be a child. The child may be suffering from acute lymphoblastic leukemia. The subject may be less than 6 months old. The subject may be about 1 year old, about 2 years old, about 3 years old, about 4 years old, about 5 years old, about 6 years old, about 7 years old, about 8 years old, about 9 years old, about 10 years old, about 11 years old, about 12 years old,

about 13 years old, about 14 years old, about 15 years old, about 18 years old, about 20 years old, about 25 years old, about 30 years old, about 35 years old, about 40 years old, about 45 years old, about 50 years old, about 55 years old, about 60 years old, about 65 years old, about 70 years old, about 75 years old, about 80 years old, about 85 years old, about 90 years old, about 95 years old, about 100 years old or about 105 years old.

VII. Method of Clearing Effector Cells

[0145] Further disclosed herein are methods of clearing CAR-EC cells in a subject, comprising administering a CAR-EC off switch. The CAR-EC off switch may comprise an antibody or antibody fragment that targets a cell surface marker on the effector cell. The CAR-EC off switch may comprise a peptide that is bound by the CAR of the CAR-EC. The CAR-EC off switch may comprise a CAR-BP that is bound by the CAR of the CAR-EC.

[0146] The antibody, antibody fragment or peptide of the CAR-EC off switch may be conjugated to a drug or a toxin. The drug or toxin may be selected from maytasine (e.g. DM1, DM4), monomethylauristatin E, monomethylauristatin F, Ki-4.dgA, dolastatin 10, calicheamicin, SN-38, duocarmycin, irinotecan, ricin, saporin, gelonin, poke weed antiviral protein, pseudomonas aeruginosa exotoxin A or diphtheria toxin. The toxin may comprise a poison, a bacterial toxin (e.g. bacterial toxins causing tetanus, diphtheria), a plant toxin or animal toxin. The toxin may be a snake venom. The toxin may comprise vinblastine. The toxin may comprise auristatin. The toxin may be contained in a liposome membrane-coated vesicle. Wherein the toxin is contained in a liposome membrane-coated vesicle, the antibody is attached to the vesicle.

[0147] The cell surface marker may be a viral protein or fragment thereof. Alternatively or additionally, the effector cell expresses a viral protein or fragment thereof that is not a cell surface marker. The effector cell expressing a viral protein or fragment thereof may be targeted with a drug. Wherein the effector cell comprises a viral protein or fragment thereof, the drug may be selected from a group comprising abacavir, acyclovir, acyclovir, adefovir, amantadine, amprenavir, ampligen, arbidol, atazanavir, atripla, balavir, boceprevirertet, cidofovir, combivir, darunavir, delavirdine, didanosine, docosanol, edoxudine, efavirenz, emtricitabine, enfuvirtide, entecavir, an entry inhibitor, famciclovir, a fixed dose combination antiretroviral drug, fomivirsen, fosamprenavir, foscarnet, fosfonet, a fusion inhibitor, ganciclovir, ibacitabine, imunovir, idoxuridine, imiquimod, indinavir, inosine, integrase inhibitor, interferon type III, interferon type II, interferon type I, interferon, lamivudine, lopinavir, loviride, maraviroc, moroxydine, methisazone, nelfinavir, nevirapine, nexavir, nucleoside analogue, oseltamivir, peginterferon alfa-2a, penciclovir, peramivir, pleconaril, podophyllotoxin, protease inhibiro, raltegravir, a reverse transcriptase inhibitor, ribavirin, rimantadine, ritonavir, pyramidine, saquinavir, sofosbuvir, stavudine, a synergistic enhancer retroviral durg, tea tree oil, telaprevir, tenofovir, tenofovir disoproxil, tipranavir, trifluridine, trizivir, tromantadine, truvada, valaciclovir, vicriviroc, vidarabine, viramidine, zacitabine, zanamivir or zidovudine. The drug may be ganciclovir. The drug may be acyclovir.

VIII. Pharmaceutical Compositions

[0148] Disclosed herein is a pharmaceutical composition comprising one or more of the CAR-EC switches disclosed herein. The compositions may further comprise one or more pharmaceutically acceptable salts, excipients or vehicles. Pharmaceutically acceptable salts, excipients, or vehicles for use in the present pharmaceutical compositions include carriers, excipients, diluents, antioxidants, preservatives, coloring, flavoring and diluting agents, emulsifying agents, suspending agents, solvents, fillers, bulking agents, buffers, delivery vehicles, tonicity agents, cosolvents, wetting agents, complexing agents, buffering agents, antimicrobials, and surfactants.

[0149] Neutral buffered saline or saline mixed with serum albumin are exemplary appropriate carriers. The pharmaceutical compositions may include antioxidants such as ascorbic acid; low molecular weight polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as Tween, pluronics, or polyethylene glycol (PEG). Also by way of example, suitable tonicity enhancing agents include alkali metal halides (preferably sodium or potassium chloride), mannitol, sorbitol, and the like. Suitable preservatives include benzalkonium chloride, thimerosal, phenethyl alcohol, methylparaben, propylparaben, chlorhexidine, sorbic acid and the like. Hydrogen peroxide also may be used as preservative. Suitable cosolvents include glycerin, propylene glycol, and PEG. Suitable complexing agents include caffeine, polyvinylpyrrolidone, beta-cyclodextrin or hydroxy-propyl-beta-cyclodextrin. Suitable surfactants or wetting agents include sorbitan esters, polysorbates such as polysorbate 80, tromethamine, lecithin, cholesterol, tyloxapal, and the like. The buffers may be conventional buffers such as acetate, borate, citrate, phosphate, bicarbonate, or Tris-HCl. Acetate buffer may be about pH 4-5.5, and Tris buffer may be about pH 7-8.5. Additional pharmaceutical agents are set forth in Remington's Pharmaceutical Sciences, 18th Edition, A. R. Gennaro, ed., Mack Publishing Company, 1990.

[0150] The composition may be in liquid form or in a lyophilized or freeze-dried form and may include one or more lyoprotectants, excipients, surfactants, high molecular weight structural additives and/or bulking agents (see, for example, U.S. Pat. Nos. 6,685,940, 6,566,329, and 6,372,716). In one embodiment, a lyoprotectant is included, which is a non-reducing sugar such as sucrose, lactose or trehalose. The amount of lyoprotectant generally included is such that, upon reconstitution, the resulting formulation will be isotonic, although hypertonic or slightly hypotonic formulations also may be suitable. In addition, the amount of lyoprotectant should be sufficient to prevent an unacceptable amount of degradation and/or aggregation of the protein upon lyophilization. Exemplary lyoprotectant concentrations for sugars (e.g., sucrose, lactose, trehalose) in the pre-lyophilized formulation are from about 10 mM to about 400 mM. In another embodiment, a surfactant is included, such as for example, nonionic surfactants and ionic surfactants such as polysorbates (e.g., polysorbate

20, polysorbate 80); poloxamers (e.g., poloxamer 188); poly(ethylene glycol) phenyl ethers (e.g., Triton); sodium dodecyl sulfate (SDS); sodium laurel sulfate; sodium octyl glycoside; lauryl-, myristyl-, linoleyl-, or stearyl-sulfobetaine; lauryl-, myristyl-, linoleyl-or stearyl-sarcosine; linoleyl, myristyl-, or cetyl-betaine; lauroamidopropyl-, cocamidopropyl-, linoleamidopropyl-, myristamidopropyl-, palmidopropyl-, or isostearamidopropyl-betaine (e.g., lauroamidopropyl); myristamidopropyl-, palmidopropyl-, or isostearamidopropyl-dimethylamine; sodium methyl cocoyl-, or disodium methyl ofeyl-taurate; and the MONAQUAT®. series (Mona Industries, Inc., Paterson, N.J.), polyethyl glycol, polypropyl glycol, and copolymers of ethylene and propylene glycol (e.g., Pluronics, PF68 etc). Exemplary amounts of surfactant that may be present in the pre-lyophilized formulation are from about 0.001-0.5%. High molecular weight structural additives (e.g., fillers, binders) may include for example, acacia, albumin, alginic acid, calcium phosphate (dibasic), cellulose, carboxymethylcellulose, carboxymethylcellulose sodium, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, microcrystalline cellulose, dextran, dextrin, dextrates, sucrose, tylose, pregelatinized starch, calcium sulfate, amylose, glycine, bentonite, maltose, sorbitol, ethylcellulose, disodium hydrogen phosphate, disodium phosphate, disodium pyrosulfite, polyvinyl alcohol, gelatin, glucose, guar gum, liquid glucose, compressible sugar, magnesium aluminum silicate, maltodextrin, polyethylene oxide, polymethacrylates, povidone, sodium alginate, tragacanth microcrystalline cellulose, starch, and zein. Exemplary concentrations of high molecular weight structural additives are from 0.1% to 10% by weight. In other embodiments, a bulking agent (e.g., mannitol, glycine) may be included.

[0151] Compositions may be suitable for parenteral administration. Exemplary compositions are suitable for injection or infusion into an animal by any route available to the skilled worker, such as intraarticular, subcutaneous, intravenous, intramuscular, intraperitoneal, intracerebral (intraparenchymal), intracerebroventricular, intramuscular, intraocular, intraarterial, or intralesional routes. A parenteral formulation typically will be a sterile, pyrogen-free, isotonic aqueous solution, optionally containing pharmaceutically acceptable preservatives.

[0152] Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Parenteral vehicles include sodium chloride solution, Ringers' dextrose, dextrose and sodium chloride, lactated Ringer's, or fixed oils. Intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers, such as those based on Ringer's dextrose, and the like. Preservatives and other additives may also be present, such as, for example, anti-microbials, anti-oxidants, chelating agents, inert gases and the like. See generally, Remington's Pharmaceutical Science, 16th Ed., Mack Eds., 1980.

[0153] Pharmaceutical compositions described herein may be formulated for controlled or sustained delivery in a manner that provides local concentration of the product (e.g., bolus, depot effect) and/or increased stability or half-life in a particular local environment. The compositions may comprise the formulation of CAR-EC switches, polypeptides, nucleic acids, or vectors disclosed herein with particulate preparations of polymeric compounds such as polylactic acid, polyglycolic acid, etc., as well as agents such as a biodegradable matrix, injectable microspheres, microcapsular particles, microcapsules, bioerodible particles beads, liposomes, and implantable delivery devices that provide for the controlled or sustained release of the active agent which then may be delivered as a depot injection. Techniques for formulating such sustained-or controlled-delivery means are known and a variety of polymers have been developed and used for the controlled release and delivery of drugs. Such polymers are typically biodegradable and biocompatible. Polymer hydrogels, including those formed by complexation of enantiomeric polymer or polypeptide segments, and hydrogels with temperature or pH sensitive properties, may be desirable for providing drug depot effect because of the mild and aqueous conditions involved in trapping bioactive protein agents (e.g., antibodies comprising an ultralong CDR3). See, for example, the description of controlled release porous polymeric microparticles for the delivery of pharmaceutical compositions in WO 93/15722. Suitable materials for this purpose include polylactides (see, e.g., U.S. Pat. No. 3,773,919), polymers of poly-(a-hydroxycarboxylic acids), such as poly-D-(-)-3-hydroxybutyric acid (EP 133,988A), copolymers of L-glutamic acid and gamma ethyl-L-glutamate (Sidman et al., Biopolymers, 22: 547-556 (1983)), poly(2-hydroxyethylmethacrylate) (Langer et al., J. Biomed. Mater. Res., 15: 167-277 (1981), and Langer, Chem. Tech., 12: 98-105 (1982)), ethylene vinyl acetate, or poly-D(-)-3-hydroxybutyric acid. Other biodegradable polymers include poly(lactones), poly(acetals), poly(orthoesters), and poly(orthocarbonates). Sustained-release compositions also may include liposomes, which may be prepared by any of several methods known in the art (see, e.g., Eppstein et al., Proc. Natl. Acad. Sci. USA, 82: 3688-92 (1985)). The carrier itself, or its degradation products, should be nontoxic in the target tissue and should not further aggravate the condition. This may be determined by routine screening in animal models of the target disorder or, if such models are unavailable, in normal animals. Microencapsulation of recombinant proteins for sustained release has been performed successfully with human growth hormone (rhGH), interferon-(rhIFN-), interleukin-2, and MN rgp 120. Johnson et al., Nat. Med., 2:795-799 (1996); Yasuda, Biomed. Ther., 27:1221-1223 (1993); Hora et al., Bio/Technology. 8:755-758 (1990); Cleland, "Design and Production of Single Immunization Vaccines Using Polylactide Polyglycolide Microsphere Systems," in Vaccine Design: The Subunit and Adjuvant Approach, Powell and Newman, eds, (Plenum Press: New York, 1995), pp. 439-462; WO 97/03692, WO 96/40072, WO 96/07399; and U.S. Patent No. 5,654,010. The sustained-release formulations of these proteins were developed using poly-lacticcoglycolic acid (PLGA) polymer due to its biocompatibility and wide range of biodegradable properties. The degradation products of PLGA, lactic and glycolic acids may be cleared quickly within the human body. Moreover, the degradability of this polymer may be depending on its molecular weight and composition. Lewis, "Controlled release of bioactive agents from lactide/glycolide polymer," in: M. Chasin and R. Langer (Eds.), Biodegradable Polymers as Drug Delivery Systems (Marcel Dekker: New York, 1990), pp. 1-41. Additional examples of sustained release compositions include, for example, EP 58,481A, U.S. Pat. No.

3,887,699, EP 158,277A, Canadian Patent No. 1176565, U. Sidman et al., Biopolymers 22, 547 [1983], R. Langer et al., Chem. Tech. 12, 98 [1982], Sinha et al., J. Control. Release 90, 261 [2003], Zhu et al., Nat. Biotechnol. 18, 24 [2000], and Dai et al., Colloids Surf B Biointerfaces 41, 117 [2005].

[0154] Bioadhesive polymers are also contemplated for use in or with compositions of the present disclosure. Bioadhesives are synthetic and naturally occurring materials able to adhere to biological substrates for extended time periods. For example, Carbopol and polycarbophil are both synthetic cross-linked derivatives of poly(acrylic acid). Bioadhesive delivery systems based on naturally occurring substances include for example hyaluronic acid, also known as hyaluronan. Hyaluronic acid is a naturally occurring mucopolysaccharide consisting of residues of D-glucuronic and N-acetyl-D-glucosamine. Hyaluronic acid is found in the extracellular tissue matrix of vertebrates, including in connective tissues, as well as in synovial fluid and in the vitreous and aqueous humor of the eye. Esterified derivatives of hyaluronic acid have been used to produce microspheres for use in delivery that are biocompatible and biodegradable (see, for example, Cortivo et al., Biomaterials (1991) 12:727-730; EP 517,565; WO 96/29998; Illum et al., J. Controlled Rel. (1994) 29:133-141).

[0155] Both biodegradable and non-biodegradable polymeric matrices may be used to deliver compositions of the present disclosure, and such polymeric matrices may comprise natural or synthetic polymers. Biodegradable matrices are preferred. The period of time over which release occurs is based on selection of the polymer. Typically, release over a period ranging from between a few hours and three to twelve months is most desirable. Exemplary synthetic polymers which may be used to form the biodegradable delivery system include: polymers of lactic acid and glycolic acid, polyamides, polycarbonates, polyalkylenes, polyalkylene glycols, polyalkylene oxides, polyalkylene terepthalates, polyvinyl alcohols, polyvinyl ethers, polyvinyl esters, poly-vinyl halides, polyvinylpyrrolidone, polyglycolides, polysiloxanes, polyanhydrides, polyurethanes and co-polymers thereof, poly(butic acid), poly(valeric acid), alkyl cellulose, hydroxyalkyl celluloses, cellulose ethers, cellulose esters, nitro celluloses, polymers of acrylic and methacrylic esters, methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxybutyl methyl cellulose, cellulose acetate, cellulose propionate, cellulose acetate butyrate, cellulose acetate phthalate, carboxylethyl cellulose, cellulose triacetate, cellulose sulphate sodium salt, poly(methyl methacrylate), poly(ethyl methacrylate), poly(butylmethacrylate), poly(isobutyl methacrylate), poly(hexylmethacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate), polyethylene, polypropylene, poly(ethylene glycol), poly(ethylene oxide), poly(ethylene terephthalate), poly(vinyl alcohols), polyvinyl acetate, poly vinyl chloride, polystyrene and polyvinylpyrrolidone. Exemplary natural polymers include alginate and other polysaccharides including dextran and cellulose, collagen, chemical derivatives thereof (substitutions, additions of chemical groups, for example, alkyl, alkylene, hydroxylations, oxidations, and other modifications routinely made by those skilled in the art), albumin and other hydrophilic proteins, zein and other prolamines and hydrophobic proteins, copolymers and mixtures thereof. In general, these materials degrade either by enzymatic hydrolysis or exposure to water in vivo, by surface or bulk erosion. The polymer optionally is in the form of a hydrogel (see, for example, WO 04/009664, WO 05/087201, Sawhney, et al., Macromolecules, 1993, 26, 581-587) that can absorb up to about 90% of its weight in water and further, optionally is cross-linked with multi-valent ions or other polymers.

[0156] Delivery systems also include non-polymer systems that are lipids including sterols such as cholesterol, cholesterol esters and fatty acids or neutral fats such as mono-di-and triglycerides; hydrogel release systems; silastic systems; peptide based systems; wax coatings; compressed tablets using conventional binders and excipients; partially fused implants; and the like. Specific examples include, but are not limited to: (a) erosional systems in which the product is contained in a form within a matrix such as those described in U.S. Pat. Nos. 4,452,775, 4,675,189 and 5,736,152 and (b) diffusional systems in which a product permeates at a controlled rate from a polymer such as described in U.S. Pat. Nos. 3,854,480, 5,133,974 and 5,407,686. Liposomes containing the product may be prepared by methods known methods, such as for example (DE 3,218,121; Epstein et al., Proc. Natl. Acad. Sci. USA, 82: 3688-3692 (1985); Hwang et al., Proc. Natl. Acad. Sci. USA, 77: 4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; JP 83-118008; U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324).

[0157] Alternatively or additionally, the compositions may be administered locally via implantation into the affected area of a membrane, sponge, or other appropriate material on to which a CAR-EC switch disclosed herein has been absorbed or encapsulated. Where an implantation device is used, the device may be implanted into any suitable tissue or organ, and delivery of a CAR-EC switch, nucleic acid, or vector disclosed herein may be directly through the device via bolus, or via continuous administration, or via catheter using continuous infusion.

[0158] A pharmaceutical composition comprising a CAR-EC switch disclosed herein may be formulated for inhalation, such as for example, as a dry powder. Inhalation solutions also may be formulated in a liquefied propellant for aerosol delivery. In yet another formulation, solutions may be nebulized. Additional pharmaceutical composition for pulmonary administration include, those described, for example, in WO 94/20069, which discloses pulmonary delivery of chemically modified proteins. For pulmonary delivery, the particle size should be suitable for delivery to the distal lung. For example, the particle size may be from 1 μm to 5 μm; however, larger particles may be used, for example, if each particle is fairly porous.

[0159] Certain formulations containing CAR-EC switches disclosed herein may be administered orally. Formulations administered in this fashion may be formulated with or without those carriers customarily used in the compounding of solid dosage forms such as tablets and capsules. For example, a capsule may be designed to release the active portion of the formulation at the point in the gastrointestinal tract when bioavailability is maximized and pre-systemic degradation is minimized. Additional agents may be included to facilitate absorption of a selective binding agent. Diluents, flavorings, low melting point waxes, vegetable oils, lubricants, suspending agents, tablet disintegrating agents, and binders also may be employed.

[0160] Another preparation may involve an effective quantity of a CAR-EC switch disclosed herein in a mixture with non-toxic excipients which are suitable for the manufacture of tablets. By dissolving the tablets in sterile water, or another appropriate vehicle, solutions may be prepared in unit dose form. Suitable excipients include, but are not limited to, inert diluents, such as calcium carbonate, sodium carbonate or bicarbonate, lactose, or calcium phosphate; or binding agents, such as starch, gelatin, or acacia; or lubricating agents such as magnesium stearate, stearic acid, or talc.

[0161] Suitable and/or preferred pharmaceutical formulations may be determined in view of the present disclosure and general knowledge of formulation technology, depending upon the intended route of administration, delivery format, and desired dosage. Regardless of the manner of administration, an effective dose may be calculated according to patient body weight, body surface area, or organ size. Further refinement of the calculations for determining the appropriate dosage for treatment involving each of the formulations described herein are routinely made in the art and is within the ambit of tasks routinely performed in the art. Appropriate dosages may be ascertained through use of appropriate dose-response data.

IX. CAR-EC Switch Production Methods

[0162] Disclosed herein are methods of producing CAR-EC switches comprising expressing one or more polypeptides from one or more vectors comprising one or more polynucleotide having one or more sequences that encode a chimeric antigen receptor-effector cell switch or a portion thereof, wherein the chimeric antigen receptor-effector cell switch comprises a peptidic antigen (CAR-BP) and a targeting polypeptide. The targeting moiety may comprise a targeting polypeptide. In general, the methods comprise fusing or grafting a polynucleotide encoding the CAR-BP to a polynucleotide encoding the targeting polypeptide. Fusing or grafting may be carried out by any standard cloning method known to one skilled in the art. Fusing or grafting the polynucleotides encoding the CAR-BP and targeting polypeptide may comprise enzymatic digestion of the polynucleotides, ligation of the polynucleotides and/or amplification of the polynucleotides.

[0163] The peptidic antigen may be fused to an N terminus of the targeting polypeptide. The peptidic antigen may be fused to a C terminus of the targeting polypeptide. The peptidic antigen may be grafted within the targeting polypeptide. The targeting polypeptide may comprise a targeting antibody or antibody fragment. The peptidic antigen may be fused to an N terminus of the targeting antibody or antibody fragment. The peptidic antigen may be fused to a C terminus of the targeting antibody or antibody fragment.

[0164] As used herein, the term "fused" may refer to adjoining a terminus of the CAR-BP with a terminus of the targeting polypeptide. The CAR-BP may be fused to the terminus of the targeting polypeptide without replacing or removing any amino acids of the targeting polypeptide. Fusing the CAR-BP to the terminus of the targeting polypeptide may comprise removing or replacing amino acids at the terminus of the targeting polypeptide. Removing or replacing amino acids at the terminus of the targeting polypeptide may comprise removing or replacing about 1 to about 20 amino acids at the terminus of the targeting polypeptide. The CAR-BP may be fused to the terminus of the targeting polypeptide via a linker. The linker may be fused to the CAR-BP to produce a CAR-BP-linker intermediate. The linker may be fused to a CAR-BP N terminus to produce the CAR-BP-linker intermediate. The linker may be fused to a CAR-BP C terminus to produce the CAR-BP-linker intermediate. The CAR-BP-linker intermediate may be fused to the targeting polypeptide. The CAR-BP-linker intermediate may be fused to the N terminus of the targeting polypeptide. The CAR-BP-linker intermediate may be fused to the C terminus of the targeting polypeptide. A first CAR-BP linker intermediate may be fused to the N terminus of the targeting polypeptide and a second CAR-BP linker intermediate may be fused to the C terminus of the targeting polypeptide. The CAR-BP of the first CAR-BP linker intermediate may be the same or similar to the CAR-BP of the second CAR-BP linker intermediate. The CAR-BP of the first CAR-BP linker intermediate may be different from the CAR-BP of the second CAR-BP linker intermediate.

[0165] As used herein, the term "grafted" may refer to inserting a CAR-BP within a targeting polypeptide (e.g. between two amino acids of the targeting polypeptide). The CAR-BP may be grafted within the targeting polypeptide without replacing or removing any amino acids of the targeting polypeptide. Grafting the CAR-BP within the targeting polypeptide may comprise removing or replacing amino acids within the targeting polypeptide. Removing or replacing amino acids within the targeting polypeptide may comprise removing or replacing about 1 to about 20 amino acids within the targeting polypeptide. The CAR-BP may be grafted within the targeting polypeptide via one linker. The CAR-BP may be grafted within the targeting polypeptide via two linkers. The linker may be fused to the CAR-BP N terminus to produce a CAR-BP-linker intermediate. The linker may be fused to the CAR-BP C terminus to produce a CAR-BP-linker intermediate. A first linker may be fused to the CAR-BP N terminus and a second linker may be fused to the CAR-BP C terminus to produce a CAR-BP-linker intermediate. The CAR-BP linker intermediate may be grafted with in the targeting polypeptide. A first CAR-BP linker intermediate may be grafted within the targeting polypeptide and a second CAR-BP linker intermediate may be grafted within the targeting polypeptide. The first CAR-BP linker intermediate may be grafted within a first domain of the targeting polypeptide and a second CAR-BP linker intermediate may be grafted within a second domain of the targeting polypeptide. The first domain of the targeting polypeptide may be the same as the second domain of the targeting polypeptide. The first domain of the targeting polypeptide may be different from the second domain of the targeting polypeptide. The CAR-BP of the first CAR-BP linker intermediate may be the same or similar to the CAR-BP of the second CAR-BP linker intermediate. The CAR-BP of the first CAR-BP linker intermediate may be different from the CAR-BP of the second CAR-BP linker intermediate. Unless otherwise specified, the terms "graft" and "insert", as used herein, are used interchangeably.

[0166] The targeting moiety may comprise an antibody or antibody fragment. The antibody or antibody fragment may comprise a heavy chain and a light chain or fragments thereof. The methods may comprise expressing a heavy chain wherein the peptidic antigen is fused to a terminus of the heavy chain. The methods may comprise expressing a heavy chain wherein the peptidic antigen is grafted within the heavy chain. The methods may comprise expressing a

light chain wherein the peptidic antigen is fused to a terminus of the light chain. The methods may comprise expressing a light chain wherein the peptidic antigen is grafted within the light chain.

[0167] The methods may further comprise cloning one or more polynucleotides encoding the targeting polypeptide and/or the peptidic antigen into an expression vector. The methods may further comprise ligation of the one or more polynucleotides encoding the targeting polypeptide and/or peptidic antigen into an expression vector. The expression vector may be a prokaryotic expression vector. The expression vector may be a eukaryotic expression vector. The expression vector may be a mammalian expression vector. The expression vector may be a viral expression vector. The methods may further comprise validating the cloning of the one or more polynucleotides encoding the targeting polypeptide and/or peptidic antigen into the expression vector comprising sequencing the expression vector, running gel electrophoresis of the vector and/or viewing the targeting polypeptide and/or peptidic antigen on an SDS page gel.

[0168] The methods may further comprise amplifying a polynucleotide encoding the targeting polypeptide and/or peptidic antigen and cloning the targeting polypeptide and/or peptidic antigen into the expression vector. Amplifying the polynucleotide encoding the targeting polypeptide and/or the peptidic antigen may comprise synthesizing oligonucleotides at least partially complementary to the gene. The oligonucleotides may be sufficiently complementary to the gene to anneal to the polynucleotide. The oligonucleotides may comprise linker sequences. The linker sequences may be selected from SEQ ID NOs: 40-44.

[0169] The methods may further comprise transfecting or infecting a cell with the expression vector. The methods may further comprise expressing the targeting polypeptide and/or peptidic antigen in the cell. The methods may further comprise expressing the targeting polypeptide and/or peptidic antigen in a cell free system. The methods may further comprise producing a virus comprising the expression vector. The methods may further comprise propagating the virus. The methods may further comprise infecting a cell with the virus comprising the expression vector. The methods may further comprise propagating the cell.

[0170] Disclosed herein are methods of grafting the antibody or antibody fragment, the peptidic antigen or the targeting peptide to produce a CAR-EC switch. The method may comprise grafting the CAR-BP to the antibody or antibody fragment. The method may comprise grafting the CAR-BP to an N terminus, C terminus or internal site of the antibody or antibody fragment. The CAR-BP may be grafted to a CL domain of the antibody or antibody fragment. The CAR-BP may be grafted to a loop of the CL domain of the antibody or antibody fragment. The method may comprise grafting the antibody or antibody fragment to the CAR-BP. The method may comprise grafting the antibody or antibody fragment to an N terminus, C terminus or internal site of the CAR-BP. The method may comprise grafting the CAR-BP to the targeting peptide. The method may comprise grafting the CAR-BP to an N terminus, C terminus or internal site of the targeting peptide. The method may comprise grafting the targeting peptide to the CAR-BP. The method may comprise grafting the targeting peptide to an N terminus, C terminus or internal site of the CAR-BP.

[0171] The CAR-BP, targeting peptide, antibody or antibody fragment may comprise one or more linkers, wherein the linker is located at the N terminus and/or C terminus of the CAR-BP, targeting peptide, antibody or antibody fragment. The method may comprise grafting the antibody or antibody fragment, the CAR-BP or the targeting peptide through the linker. The linker may comprise $(GSSSS)_n$.

[0172] Grafting may comprise producing a CAR-EC switch encoding nucleic acid. Producing the CAR-EC switch encoding nucleic acid may comprise one or more polymerase chain reactions. Producing the CAR-EC switch encoding nucleic acid may comprise one or more nucleic acid enzymatic digestions. The enzymatic digestion may be site specific. Producing the CAR-EC switch encoding nucleic acid may comprise one or more ligations. The methods of producing the CAR-EC switch may comprise incorporating the CAR-EC switch encoding nucleic acid into a CAR-EC switch vector. The vector may be an expression vector. The expression vector may comprise a constitutive promoter, an inducible promoter and/or a conditional promoter. The CAR-EC switch encoding nucleic acid or CAR-EC switch vector may be expressed in a cell and the resulting CAR-EC switch isolated and purified. The cell may be a prokaryotic cell. The cell may be an *E.coli*. The cell may be a eukaryotic cell. The cell may be a mammalian cell. The CAR-EC switch encoding nucleic acid or CAR-EC switch vector may be expressed in a cell-free system. Alternatively or additionally the CAR-EC switch may be synthesized from free amino acids.

Purification of CAR-EC Switches and Portions Thereof

[0173] Disclosed herein are methods of purifying CAR-EC switches disclosed herein, comprising separating the CAR-EC switches disclosed herein from components of a CAR-EC switch production system (e.g. cellular debris, free amino acids). Purifying the CAR-EC switch may comprise use of one or more concentrator columns, electrophoresis, filtration, centrifugation, chromatography or a combination thereof. Chromatography may comprise size-exclusion chromatography. Additional chromatography methods include, but are not limited to, hydrophobic interaction chromatography, ion exchange chromatography, affinity chromatography, metal binding, immunoaffinity chromatography, and high performance liquid chromatography or high pressure liquid chromatography. Electrophoresis may comprise denaturing electrophoresis or non-denaturing electrophoresis.

[0174] The CAR-EC switches may comprise one or more peptide tags. The methods of purifying CAR-EC switches may comprise binding one or more peptide tags of the CAR-EC switches to a capturing agent. The capturing agent may be selected from an antibody, a column, a bead and a combination thereof. The one or more tags may be cleaved by one or more proteases. Examples of tags include, but are not limited to, polyhistidine, FLAG® tag, HA, c-myc, V5, chitin binding protein (CBP), maltose binding protein (MBP), and glutathione-S-transferase (GST). The peptide tag may be the CAR-BP. The peptide tag may be HTP. The peptide tag may be yeast transcription factor GCN4.

[0175] The methods may further comprise lyophilization or ultracentrifugation of the CAR-BPs, targeting polypeptides and/or the CAR-EC switches.

[0176] The purity of the CAR-BPs, targeting polypeptides and/or the CAR-EC switches may be equal to or greater than 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more. The purity of the CAR-BPs, targeting polypeptides and/or the CAR-EC switches may be equal to or greater than 85%. The purity of the CAR-BPs, targeting polypeptides and/or the CAR-EC switches may be equal to or greater than 90%. The purity of the CAR-BPs, targeting polypeptides and/or the CAR-EC switches may be equal to or greater than 95%. The purity of the CAR-BPs, targeting polypeptides and/or the CAR-EC switches may be equal to or greater than 97%.

[0177] The methods of producing CAR-EC switches disclosed herein may comprise producing CAR-EC switches that are structurally homogeneous. The method of producing the CAR-EC switch from a polynucleotide may result in one or more CAR-EC switches that have the same or similar form, features, binding affinities (e.g. for the CAR or the target), geometry and/or size. The homogeneity of the CAR-EC switches may be equal to or greater than 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more. The homogeneity of the CAR-EC switches may be equal to or greater than 85%. The homogeneity CAR-EC switches may be equal to or greater than 90%. The homogeneity of the CAR-EC switches may be equal to or greater than 95%. The homogeneity of the CAR-EC switches may be equal to or greater than 97%. The homogeneity may be a structural homogeneity. The homogeneity may be a structural homogeneity prior to administering the cell to a subject. The homogeneity may be a structural homogeneity prior to modifications to the CAR-EC switch by cellular activities (methylation, acetylation, glycosylation, etc.). These high percentages of homogeneity may provide a more predictable effect of the CAR-EC switch. These high percentages of homogeneity may provide for less off-target effects of the CAR-EC switch, when combined with a CAR-EC to treat a condition in a subject.

EXAMPLES

[0178] The following illustrative examples are representative of embodiments of the software applications, systems, and methods described herein and are not meant to be limiting in any way.

Example 1 - Production and Evaluation of a Switchable CAR-T Platform

[0179] The solubility, stability, affinity, and potential for cross reactive epitopes in the human proteome of developed antibodies were considered in choosing a CAR-EC switch peptidic antigen. Based on these criteria, a linear amino acid epitope from the yeast transcription factor GCN4 (7P14P) was chosen. Single chain antibodies with affinities varying from 2.6 nM to 5.2 pM enable optimization of the CAR-EC through binding kinetics. Additionally, these antibodies are among the highest affinity anti-peptide single chain antibodies for linear epitopes. The dissociation constant (Kd) for the chosen GCN4 epitope (7P14P) having a sequence of NYHLENEVARLKKL (SEQ ID NO. 3) and GCN4 binding scFv (52SR4) is 5.2 pM.

[0180] A small hydrophilic target peptide (HTP), based on the commonly used FLAG® tag, was developed. FLAG® has low antigenicity, is highly soluble, and has been fused to numerous proteins with little impact on protein folding or stability. In modifying FLAG to HTP, a proline residue was incorporated after the terminal lysine in an effort to increase proteolytic stability. Antibodies to this epitope are developed by traditional mouse immunization and subsequent humanization or by phage panning of a human library. Binding kinetics of evolved scFv's are fully characterized and peptide-CAR-ECs are created and tested for off-target specificity as described.

Evaluation of a Switchable CAR-T Platform in a Xenograft Model

[0181] To evaluate efficacy, mouse xenograft models are used to compare these switchable platforms to previously developed by CAR-T switch platforms. Towards this end, RS4; 11, NALM-6, Raji or other CD19 positive cell lines are used to establish tumor models in nonobese diabetic-severe combined immunodeficiency (NOD-SCID-$\gamma^{-/-}$, NSG) mice. CAR-Ts are delivered by intravenous administration. Dose-range finding is carried out for the peptide anti-CD19 switch, and is compared to a wild type CD19 Fab control. Efficacy is judged based on tumor burden and overall survival. Mice are monitored with weekly blood draws to monitor proliferation of CAR-ECs in peripheral blood. Detailed immunophenotypic characterization of CAR-ECs focus on effector, memory, senescent (terminally differentiated), or anergized phenotypes are defined according to standard phenotypic parameters using multi-channel flow cytometry.

[0182] Efficacy of the Fab, and IgG based switches are delivered at appropriate dosages per observed PK data and compared. IgG is most efficacious in this model for its long residence time in vivo. Further exploration on this idea is carried out in the syngeneic model.

[0183] Primary patient-derived ALL or CLL samples are obtained and for generating xenograft models in NSG mice. Primary samples are characterized for CD19 expression by flow cytometry. Leukemia is established in mice for 2-3 weeks prior to administration of therapy. Efficacy versus CAR-T-19 is judged by monitoring $CD19^{+}$ ALL blast counts in peripheral blood. In the event that leukemia is not controlled or eliminated, proliferated blasts are immunophenotyped (specifically looking for loss of CD19 antigen expression, vida infra for further study). Persistence of CAR-ECs is also monitored (although the latter is not expected to differ substantially from RS4;11-based xenografts).

Evaluation of a Switchable CAR-T Platform in a Syngeneic Model

[0184] Although the xenograft models in immunodeficient mice allow measurement of the efficacy of the switchable platform, this model is not optimal to assess a method for alleviating the long-term lymphopenia associated with CAR-T-19 therapy. Switchable CAR-ECs are tested for the ability to reverse B cell aplasia in an immunocompetent B cell lymphoma mouse model. To create a murine surrogate CAR-T, the engineered peptide-based chimeric receptor is cloned to a Moloney murine leukemia-based retroviral vector for transduction into murine splenocytes. The murine-derived signaling domains CD28 and CD3z are used. The anti-human CD19 antibody does not cross-react with mouse CD19; therefore, the rat anti-mouse CD19 hybri-

doma 1D3 is obtained (from ATCC) and variable regions sequenced. This sequence is cloned into an expression vector for peptide fusion to create the switch and is cloned into a chimeric antigen receptor to create a CAR-T-19 mouse surrogate.

[0185] After optimization of transduction and assessment of efficacy in vitro, the Myc5-CD19 cell line is used to establish B cell lymphoma in wild type C57BL/6 mice. CAR-ECs and switches are administered with dosing schedules based on xenograft studies and in vitro assays with surrogate system. Of particular interest in this model is to compare Fab, and IgG based switches on the rate of Myc5-CD19 disappearance and B cell ablation. As with xenografts studies, CAR-T proliferation is monitored and immunophenotypic characterization is carried out ex vivo. After eradication of lymphoma cells, switch administration is halted and the reproliferation of B cells in peripheral blood is monitored. Both the surrogate CAR-T-19 and the surrogate switchable CAR-T are expected to enable long-term remission, but only the switchable platform enables repopulation of B cells. CAR-T infiltration to major organs is monitored via histology on predefined cohorts and cellular analysis is carried out post-therapy. Long-term persistence of CAR-ECs in the absence of stimulation is followed.

Evaluation of a Switchable CAR-T Platform in a Heterogeneous Cancer Model

[0186] A first switch containing an anti-CD19 targeting antibody and a second switch containing the anti-CD20 targeting antibody rituximab are used sequentially or simultaneously to target different antigens in the same patient using a single adoptively transferred CAR-T in an effort to combat ALL relapse attributed to a CD19 escape variant during CAR-T-19 therapy.

[0187] An anti-CD20 switch is created in analogous fashion to the anti-CD19 switch using the optimal characteristics determined in Example 3. A CAR-T-20 based on rituximab is constructed for comparison. Efficacy is tested in vitro against CD20-positive IM-9 and Daudi cells lines. To create a heterogeneous B-cell lymphoblast, the chronic myelogenous leukemia-derived K562 cell line (which is negative for CD20 and CD19) is stably transduced with the CD19 antigen using a lentiviral vector. Single cell clones are obtained via flow-sorting to obtain a population with homogenous CD19 expression. This cell line is then be transduced with CD20 and sorted by high ($CD20^{hi}$) or low ($CD20^{low}$) level of antigen expression. The activation and cytotoxicity of the switchable CAR-T on mixtures of $CD19^{+}CD20^{-}$ and $CD19^{+}CD20^{hi}$ or $CD19^{+}CD20^{low}$ are assessed in vitro using the CD19 and CD20 switches (simultaneous or sequential administration). The method provides an opportunity to study the lowest percentage of $CD20^{hi}$ or $CD20^{low}$ cells in a population that are necessary to stimulate the CAR-T with the rituximab switch. This may be more physiologically relevant than a homogeneous population. This system is then tested in a xenograft mouse model. A mixture of $CD19^{+}CD20^{-}$ and $CD19^{+}CD20^{+}$ are used to establish the xenograft. Alternatively, primary patient derived ALL samples are used for this experiment if found to be heterogeneous for CD19 or CD20 expression in our initial xenograft study. Switchable CAR-ECs with the anti-CD20 switch are administered to eliminate the $CD19^{+}CD20^{+}$ population and allow outgrowth of $CD19^{+}CD20^{-}$ cells. To demonstrate the feasibility of retargeting the same CAR-T, the anti-CD19 switch is subsequently dosed and growth of remaining xenograft monitored. Tumors are evaluated for antigen expression in cohorts of sacrificed mice or in primary blasts. Simultaneous targeting is also assessed. Treatment is compared with CAR-T-19, CAR-T-20, or both simultaneously.

Example 2. CAR Construction

[0188] The CARs were constructed as follows:

[0189] LV-EF1a-GCN4-BBZ was designed to target the 7P14P epitope of the yeast transcription factor GCN4 (sequence RMKQLEPKVEELLPKNYHLENEVARLKKLVGER (SEQ ID NO. 2) where the underlined amino acids have been shown to bind to the c11L32Ser scFv in the 1P4B crystal structure from PDB. The scFv was constructed from the 52SR4 (high affinity mutant with similar sequence to c11L32Ser) antibody scFv from reference: Zahnd, C., Spinelli, S., Luginbuhl, B., Amstutz, P., Cambillau, C., and Pluckthun, A. (2004) Directed in vitro evolution and crystallographic analysis of a peptide-binding single chain antibody fragment (scFv) with low picomolar affinity, *The Journal of Biological Chemistry* 279, 18870-18877.

Example 3. Cloning, Expression and Purification of Anti-CD19-Fab-GCN4 HCl

[0190] Cloning: Mammalian expression vector of CD19 Fab heavy chain was generated by ligation of amplified CD19 Fab heavy chain (VH and CH1) to pFuse-hIgG1-Fc backbone vector (InvivoGen, CA) without Fc fragment. A gene encoding antibody CD19 light chain was amplified and cloned into the pFuse vector without hIgG1 Fc fragment. A gene encoding GCN4 (NYHLENEVARLKKL = SEQ ID NO: 3) with was synthesized as oligonucleotides. Subsequently, anti-CD1-Fab-GCN4 $_{HCl}$ fusion proteins were created by grafting GCN4 into the mature heavy chain of the CD19 Fab following S135 of the CD19 Fab heavy chain. The resulting mammalian expression vectors were confirmed by DNA sequencing.

[0191] Expression and Purification: anti-CD19-Fab-GCN4 $_{HCl}$ was expressed through transient transfection of FreeStyle HEK 293 cells with expression vectors of CD19-Fab light chain and GCN4-CD19-HC1, according to the manufacturer's protocol. Briefly, 28 mL FreeStyle HEK 293 cells containing 3×107 cells were seeded in a 125 mL shaking flask. 15 μg light chain plasmid and 15 μg heavy chain plasmid diluted in 1 mL Opti-MEM medium were added in 1 mL Opti-MEM containing 60 μL 293fectin (Invitrogen, Inc). After the plasmids were incubated with 293fectin for 30 min, the lipoplex mixture was added to the cell suspension. Cells were then shaken at 125 rpm in a 5% CO2 environment at 37° C. Culture medium containing secreted proteins was harvested at 48 and 96 hours after transfection. The anti-CD1-Fab-GCN4 $_{HCl}$ was purified by Protein G chromatography (Thermo Fisher Scientific, IL). Purified proteins were analyzed by SDS-PAGE gels. FIGS. **5**A and **5**B show SDS gel images of anti-CD1-Fab-GCN4 $_{HCl}$ (Lane 7) in non-reducing and reducing (with 50 mM DTT) conditions, respectively.

Example 4. Cloning, Expression and Purification of Anti-CD19-IgG-GCN4 $_{HCl}$

[0192] Cloning: Mammalian expression vector of CD19 IgG heavy chain was generated by in-frame ligation of amplified CD19 Fab heavy chain (VH and CH1) to pFuse-hIgG1-Fc backbone vector (InvivoGen, CA). A gene encoding antibody CD19 light chain was amplified and cloned into the pFuse vector without hIgG1 Fc fragment. A gene encoding GCN4 (NYHLENEVARLKKL = SEQ ID NO: 3) was synthesized as oligonucleotides. Subsequently, anti-CD19-IgG-GCN4 $_{HCl}$ fusion proteins were created by inserting GCN4 following S135 of the mature heavy chain of the CD19 IgG. The resulting mammalian expression vectors were confirmed by DNA sequencing.

[0193] Expression and Purification: anti-CD19-IgG-GCN4 $_{HCl}$ was expressed through transient transfection of FreeStyle HEK 293 cells with expression vectors of CD19-IgG light chain and GCN4-CD19 heavy chain, according to the manufacturer's protocol. Briefly, 28 mL FreeStyle HEK 293 cells containing 3×107 cells were seeded in a 125 mL shaking flask. 15 μg light chain plasmid and 15 μg heavy chain plasmid diluted in 1 mL Opti-MEM medium were added in 1 mL Opti-MEM containing 60 μL 293fectin (Invitrogen, Inc). After the plasmids were incubated with 293fectin for 30 min, the lipoplex mixture was added to the cell suspension. Cells were then shaken at 125 rpm in a 5% CO2 environment at 37° C. Culture medium containing secreted proteins was harvested at 48 and 96 hours after transfection. GCN4-CD19 heavy chain was purified by Protein G chromatography (Thermo Fisher Scientific, IL). Purified proteins were analyzed by SDS-PAGE gels. FIGS. **5**A & **5**B show SDS gel images of anti-CD19-IgG-GCN4 $_{HCl}$ (Lane 3) in non-reducing and reducing (with 50 mM DTT) conditions, respectively.

Example 5. Cloning, Expression and Purification of Anti-CD19-Fab- GCN4 $_{C\text{-}term}$

[0194] Cloning: Mammalian expression vector of CD19 Fab heavy chain was generated by ligation of amplified CD19 Fab heavy chain (VH and CH1) to pFuse-hIgG1-Fc backbone vector (InvivoGen, CA) without Fc fragment. A gene encoding antibody CD19 light chain was amplified and cloned into the pFuse vector without hIgG1 Fc fragment. A gene encoding GCN4 (NYHLENEVARLKKL = SEQ ID NO: 3) with GGGGS (SEQ ID NO: 40, wherein n=1) linker at N-terminal end of GCN4 with was synthesized as oligonucleotides. Subsequently, anti-CD19-Fab- GCN4 $_{C\text{-}term}$ fusion proteins were created by fusing the linker-GCN4 to the C terminus of the Fab heavy chain at C223. The resulting mammalian expression vectors were confirmed by DNA sequencing.

[0195] Expression and Purification: anti-CD19-Fab-GCN4 $_{C\text{-}term}$ was expressed through transient transfection of FreeStyle HEK 293 cells with expression vectors of CD19-Fab light chain and anti-CD19-Fab- GCN4 $_{C\text{-}term}$, according to the manufacturer's protocol. Briefly, 28 mL FreeStyle HEK 293 cells containing 3×107 cells were seeded in a 125 mL shaking flask. 15 μg light chain plasmid and 15 μg heavy chain plasmid diluted in 1 mL Opti-MEM medium were added in 1 mL Opti-MEM containing 60 μL 293fectin (Invitrogen, Inc). After the plasmids were incubated with 293fectin for 30 min, the lipoplex mixture was added to the cell suspension. Cells were then shaken at 125 rpm in a 5% CO2 environment at 37° C. Culture medium containing secreted proteins was harvested at 48 and 96 hours after transfection. anti-CD19-Fab-GCN4 $_{C\text{-}term}$ was purified by Protein G chromatography (Thermo Fisher Scientific, IL). Purified proteins were analyzed by SDS-PAGE gels. FIGS. **5**A and **5**B show SDS gel images of anti-CD19-Fab-GCN4 $_{C\text{-}term}$ (Lane 9) in non-reducing and reducing (with 50 mM DTT) conditions, respectively.

Example 6. Cloning, Expression and Purification of Anti-CD19-IgG -GCN4$_{hinge}$

[0196] Cloning: Mammalian expression vector of CD19 IgG heavy chain was generated by in-frame ligation of amplified CD19 Fab heavy chain (VH and CH1) to pFuse-hIgG1-Fc backbone vector (InvivoGen, CA). A gene encoding antibody CD19 light chain was amplified and cloned into the pFuse vector without hIgG1 Fc fragment. A gene encoding GCN4 (NYHLENEVARLKKL = SEQ ID NO: 3) with GGGGS (SEQ ID NO: 40, wherein n=1) linker at N-terminal end of GCN4 and GGS (SEQ ID NO. 42, wherein n=1) at C-terminal of GCN4 ("linker-GCN4-linker") was synthesized as oligonucleotides. Subsequently, anti-CD19-IgG -GCN4$_{hinge}$ fusion proteins were created by grafting the linker-GCN4-linker between the C terminus of the Fab heavy chain at C223 and the hinge region. Thus, the linker-GCN4-linker extends the hinge region of the IgG, mimicking an IgG3 structure with an elongated hinge region. The resulting mammalian expression vectors were confirmed by DNA sequencing.

[0197] Expression and Purification: anti-CD19-IgG -GCN4$_{hinge}$ was expressed through transient transfection of FreeStyle HEK 293 cells with expression vectors of CD19-IgG light chain and GCN4-CD19 hinge heavy chain, according to the manufacturer's protocol. Briefly, 28 mL FreeStyle HEK 293 cells containing 3×107 cells were seeded in a 125 mL shaking flask. 15 μg light chain plasmid and 15 μg heavy chain plasmid diluted in 1 mL Opti-MEM medium were added in 1 mL Opti-MEM containing 60 μL 293fectin (Invitrogen, Inc). After the plasmids were incubated with 293fectin for 30 min, the lipoplex mixture was added to the cell suspension. Cells were then shaken at 125 rpm in a 5% CO2 environment at 37° C. Culture medium containing secreted proteins was harvested at 48 and 96 hours after transfection. GCN4-CD19 hinge IgG was purified by Protein G chromatography (Thermo Fisher Scientific, IL). Purified proteins were analyzed by SDS-PAGE gels. FIGS. **5**A & **5**B show SDS gel images of anti-CD19-IgG-GCN4$_{hinge}$ (Lane 5) in non-reducing and reducing (with 50 mM DTT) conditions, respectively.

Example 7. Cloning, Expression and Purification of Anti-CD19-IgG-GCN4$_{CL1}$

[0198] Cloning: Mammalian expression vector of CD19 IgG heavy chain was generated by in-frame ligation of amplified CD19 Fab heavy chain (VH and CH1) to pFuse-hIgG1-Fc backbone vector (InvivoGen, CA). A gene encoding antibody CD19 light chain was amplified and cloned into the pFuse vector without hIgG1 Fc fragment. A gene encoding GCN4 (NYHLENEVARLKKL = SEQ ID NO: 3) with GGGGS (SEQ ID NO: 40, wherein n=1) linker at both ends was synthesized as oligonucleotides. Subsequently, anti-CD19-IgG-GCN4$_{CL1}$ fusion proteins were created by

replacing the K169 in CL region of CD19 light chain with GCN4 with linker sequences at both ends. The resulting mammalian expression vectors were confirmed by DNA sequencing.

[0199] Expression and Purification: anti-CD19-IgG-GCN4$_{CL1}$ was expressed through transient transfection of FreeStyle HEK 293 cells with expression vectors of CD19-IgG heavy chain and GCN4-CD19-CL1 light chain, according to the manufacturer's protocol. Briefly, 28 mL FreeStyle HEK 293 cells containing 3×10^7 cells were seeded in a 125 mL shaking flask. 15 μg light chain plasmid and 15 μg heavy chain plasmid diluted in 1 mL Opti-MEM medium were added in 1 mL Opti-MEM containing 60 μL 293fectin (Invitrogen, Inc). After the plasmids were incubated with 293fectin for 30 min, the lipoplex mixture was added to the cell suspension. Cells were then shaken at 125 rpm in a 5% CO_2 environment at 37° C. Culture medium containing secreted proteins was harvested at 48 and 96 hours after transfection. anti-CD19-IgG-GCN4$_{CL1}$ was purified by Protein G chromatography (Thermo Fisher Scientific, IL). Purified proteins were analyzed by SDS-PAGE gels. FIGS. **5**A & **5**B show SDS gel images of anti-CD19-IgG-GCN4$_{CL1}$ (Lane 4) in non-reducing and reducing (with 50 mM DTT) conditions, respectively.

Example 8. Cloning, Expression and Purification of Anti-CD19-Fab-GCN4$_{CL1}$

[0200] Cloning: Mammalian expression vector of CD19 Fab heavy chain was generated by ligation of amplified CD19 Fab heavy chain (VH and CH1) to pFuse-hIgG1-Fc backbone vector (InvivoGen, CA) without Fc fragment. A gene encoding antibody CD19 light chain was amplified and cloned into the pFuse vector without hIgG1 Fc fragment. A gene encoding GCN4 (NYHLENEVARLKKL = SEQ ID NO: 3) with GGGGS (SEQ ID NO: 40, wherein n=1) linker at both ends was synthesized as oligonucleotides. Subsequently, anti-CD19-Fab-GCN4$_{CL1}$ fusion proteins were created by replacing the K169 in CL region of CD19 light chain with GCN4 with linker sequences at both ends. The resulting mammalian expression vectors were confirmed by DNA sequencing.

[0201] Expression and Purification: anti-CD19-Fab-GCN4$_{CL1}$ was expressed through transient transfection of FreeStyle HEK 293 cells with expression vectors of CD19-Fab heavy chain and GCN4-CD19-CL light chain, according to the manufacturer's protocol. Briefly, 28 mL FreeStyle HEK 293 cells containing 3×10^7 cells were seeded in a 125 mL shaking flask. 15 μg light chain plasmid and 15 μg heavy chain plasmid diluted in 1 mL Opti-MEM medium were added in 1 mL Opti-MEM containing 60 μL 293fectin (Invitrogen, Inc). After the plasmids were incubated with 293fectin for 30 min, the lipoplex mixture was added to the cell suspension. Cells were then shaken at 125 rpm in a 5% CO2 environment at 37° C. Culture medium containing secreted proteins was harvested at 48 and 96 hours after transfection. The anti-CD19-Fab-GCN4$_{CL1}$ was purified by Protein G chromatography (Thermo Fisher Scientific, IL). Purified proteins were analyzed by SDS-PAGE gels. FIGS. **5**A & **5**B show SDS gel images of anti-CD19-Fab-GCN4$_{CL1}$ (Lane 8) in non-reducing and reducing (with 50 mM DTT) conditions, respectively.

Example 9. Cloning, Expression and Purification of Anti-CD19-Fab-GCN4 $_{LC1\text{-}N\text{-}term}$

[0202] Cloning: Mammalian expression vector of CD19 Fab heavy chain was generated by ligation of amplified CD19 Fab heavy chain (VH and CH1) to pFuse-hIgG1-Fc backbone vector (InvivoGen, CA) without Fc fragment. A gene encoding antibody CD19 light chain was amplified and cloned into the pFuse vector without hIgG1 Fc fragment. A gene encoding GCN4 (NYHLENEVARLKKL = SEQ ID NO: 3) with GGGGS (SEQ ID NO: 40, wherein n=1) linker at C-terminal end of GCN4 with was synthesized as oligonucleotides. Subsequently, anti-CD19-Fab-GCN4 $_{LC1\text{-}N\text{-}term}$ fusion proteins were created by fusing the linker-GCN4 to the N terminus of the Fab light chain. The resulting mammalian expression vectors were confirmed by DNA sequencing.

[0203] Expression and Purification: anti-CD19-Fab-GCN4 $_{LC1\text{-}N\text{-}term}$ was expressed through transient transfection of FreeStyle HEK 293 cells with expression vectors of CD19-Fab light chain and GCN4-CD19-C-term, according to the manufacturer's protocol. Briefly, 28 mL FreeStyle HEK 293 cells containing 3×107 cells were seeded in a 125 mL shaking flask. 15 μg light chain plasmid and 15 μg heavy chain plasmid diluted in 1 mL Opti-MEM medium were added in 1 mL Opti-MEM containing 60 μL 293fectin (Invitrogen, Inc). After the plasmids were incubated with 293fectin for 30 min, the lipoplex mixture was added to the cell suspension. Cells were then shaken at 125 rpm in a 5% CO2 environment at 37° C. Culture medium containing secreted proteins was harvested at 48 and 96 hours after transfection. anti-CD19-Fab-GCN4 $_{LC1\text{-}N\text{-}term}$ was purified by Protein G chromatography (Thermo Fisher Scientific, IL). Purified proteins were analyzed by SDS-PAGE gels. FIGS. **5**A and **5**B show SDS gel images of anti-CD19-Fab-GCN4 $_{LC1\text{-}N\text{-}term}$ (Lane 10) in non-reducing and reducing (with 50 mM DTT) conditions, respectively.

Example 10. Cytotoxicity of Anti-CD19 Fab-GCN4 $_{CL1}$, Anti-CD19 IgG$_{FcNull}$ -GCN4 and Anti-CD19 Fab-GCN4 $_{C\text{-}term}$ CAR-EC Switches

[0204] Peptide CAR-EC switches were created by fusing 14 amino acids of the GCN4 yeast transcription factor peptide sequence 7P14P (defined in Zahnd et al. (2004) Directed in vitro evolution and crystallographic analysis of a peptide-binding single chain antibody fragment (scFv) with low picomolar affinity, *The Journal of Biological Chemistry* 279, 18870-18877). The 14 amino acids were chosen based on those defined in crystal structure 1P4B of GCN4 peptide 7P14P with scFv c11L32Ser. The switches were constructed by either fusing the GCN4 peptide sequence to the C-terminus of the heavy chain of the Fab antibody or by fusing the GCN4 peptide sequence in the CL loop of the light chain of the Fab or IgG antibody. All expressions were carried out in CHO or HEK cells.

[0205] To create a grafted GCN4 peptide based anti-CD19 CAR-T switch (SEQ ID NO: 30), the peptide NYHLENEVARLKKL (SEQ ID NO: 3), suggested to be the minimal binding epitope according to the crystal structure (PDB: 1P4B) (see FIG. **2**) from the yeast transcription factor GCN4 peptide (7P14P) RMKQLEPKVEELLPKNYHLENEVARLKKLVGER (SEQ ID NO: 2), was grafted to the

mouse anti-human CD19 Fab clone FMC63. The graft was carried out by replacing K63 (as counted from the N terminus of the constant region, which would be K169 when counting from the N terminus of the mature protein) of the light chain with the sequence GGGGSNYHLENEVARLKKLGGGGS (SEQ ID NO. 4)- the GCN4 epitope flanked by GGGGS linkers (SEQ ID NO: 40, wherein n=1). The mass spec of anti-CD19 Fab_{CL1}-GCN4 is provided below (FIG. **3**). Alternatively, the peptide is grafted to the heavy chain (SEQ ID NO: 29).

[0206] The cytotoxic activity of the anti-CD19 Fab_{CL1}-GCN4 switch was assessed with the human PBMCs transduced with LV-EF1a-GCN4(52SR4) to create CAR-T-GCN4 at E:T ratios of 10: 1 and 24 hour incubation. Activity was assessed against NALM-6 ($CD19^+$), RS4;11 ($CD19^+$), or RPMI-8226 ($CD19^-$) (Table 1). The activity of the IgG (FcNull) switch was assessed against RS4;11 ($CD19^+$), or K562 ($CD19^-$) (Table 2). The activity of the C-terminal switch was assessed against RS4;11 ($CD19^+$), or K562 ($CD19^-$) (Table 3).

TABLE 1

Cytotoxicity of the anti-CD19 Fab_{CL1}-GCN4 switch

	%Cytotoxicity		
Concentration (pM)	NALM-6 (CD19 positive)	RS4;11 (CD19 positive)	RPMI-8226 (CD19 negative)
10	86.74405	104.0488	15.20283
1	82.23607	90.00308	8.149928
0.1	77.28449	84.11992	3.819127
0.01	47.15363	45.37116	2.656606
0.001	-5.794394	-2.258805	-4.993927
0.0001	-7.191706	-8.02902	-7.662813
0.00001	-4.779683	-2.792706	-1.318068

TABLE 2

Cytotoxicity of anti-CD 19 IgG_{FcNull} -GCN4 switch

	%Cytotoxicity	
Concentration (pM)	RS4;11 (CD19 positive)	K562 (CD19 negative)
1	53.56274	6.218475
0.1	48.75237	1.844815
0.01	38.21278	-2.777584
0.001	12.10702	-2.964143
0.0001	0.1621473	-6.301391
0.00001	-0.9188344	-4.891867

TABLE 3

Cytotoxicity of anti-CD 19 $Fabc_{term}$ -GCN4 switch

	%Cytotoxicity	
Concentration (nM)	RS4;11 (CD19 positive)	K562 (CD19 negative)
10	92.10811	1.44819
1	76.75676	-3.445695
0.1	66.59459	-2.197255
0.01	60.97298	-1.348315
0.001	8.216215	-2.147315
0.0001	-2.162161	-3.046195
0.00001	1.945946	-0.299624

Example 11. Cytotoxicity of Various Anti-CD19-GCN4 CAR-EC Switches with GCN4 Grafted/Fused to Different Regions of an Anti-CD19 Antibody or Antibody Fragment

[0207] The cytotoxic activities of various anti-CD19-GCN4 CAR-EC switches grafted/fused to different regions of anti-CD19 FMC63 antibodies or antibody fragments were assessed with the human PBMCs transduced with LV-EF1a-GCN4(52SR4) to create CAR-T-GCN4 at E:T ratios of 10:1 and 24 hour incubation. Switches tested were anti-CD19 Fab_{CL1}-GCN4 ("CL1 Fab), anti-CD19-GCN4 $Fab_{C\text{-}term}$ ("C-term Fab), anti-CD19 IgG_{HC1} -GCN4 ("HC1 IgG"), anti-CD19 IgG_{CL1} -GCN4 ("CL1 IgG"), anti-CD19 IgG_{Hinge}-GCN4 ("Hinge IgG"), anti-CD19 IgG_{WT} -GCN4 ("Wt IgG"), anti-CD19 Fab_{HC1}-GCN4 ("HC1 Fab"), and anti-CD19 $Fab_{N\text{-}term\ LC1}$-GCN4 ("N-term LC1 Fab"). Activities were assessed against RS4; 11 ($CD19^+$) (FIG. **4**, Table 4). FIG. **6** depicts the grafting positions of switches described in this example. The CL1 and HC1 grafting positions were applied to both Fab and IgG formats. The N-terminus grafting is shown as grafted to the light chain, however N-terminal grafting is not restricted to the light chain or Fab and may also be grafted to the heavy chain as well as the IgG format. The C-term position on the Fab is isosteric with the hinge IgG. In this context all Fab constructs are monovalent and all IgG constructs are bivalent, but these are not a necessary requirements for CAR-EC switches in general.

TABLE 4

Cytotoxicity of anti-CD 19-GCN4 switches

Switch Conc (nM)	CL1 Fab	C-term Fab	HC1 IgG	CL1 IgG	Hinge IgG	WT IgG	HCl Fab	N-term LC1 Fab
10	70.10483	63.81551	47.46331	54.02444	67.4252	1.785714	41.07143	59.97437
1	58.28092	59.53878	39.91614	59.58702	52.76022	2.040816	43.87755	62.53738
0.1	60.54507	55.26205	39.16142	58.3228	40.62368	3.061224	44.38776	62.28107
0.01	46.96017	33.37526	28.09225	56.80573	35.0611	2.55102	20.66327	49.46604
0.001	4.444445	-2.09644	1.174004	24.18879	2.697009	2.55102	-0.2551	21.52926
0.0001	2.180294	-4.61216	-2.09644	1.685631	-5.14117	2.040817	-0.5102	3.075609
0.00001	1.425577	-3.60587	-1.09015	0.927097	-6.65823	1.785714	-0.7653	5.07E-07
1E-07	0.922432	-1.34172	0.419288	0.674253	-1.60135	1.27551	-1.27551	1.281505

Example 12. In Vivo Efficacy of anti-CD19-Fab-GCN4$_{CL1}$ CAR-EC Switch and Anti-GCN4 CAR T-cells (swiCAR T-Cells) in a Xenograft Tumor Mouse Model.

[0208] To assess swiCAR-T cell in vivo activity, a pilot study with an orthotopic (liquid) xenograft tumor model based on luciferized NALM-6 cells was conducted. In this model swiCAR T-cells demonstrated regression after just 5 days of daily treatment with 0.5 mg/kg of anti-CD19(GCN4) CL1 Fab. Treatment with the wild type anti-CD19 Fab with swiCAR T-cells were not capable of mediating tumor regression (not significant by one-way ANOVA). These results demonstrate the ability to redirect swiCAR T-cells in vivo. Experiment details: 10^6 luciferized NALM-6 cells were injected I.V. into nonobese diabetic-severe combined immunodeficiency (NOD-SCID-$\gamma^{-/-}$, NSG) mice. Six days later, 30×10^6 swiCAR T-cells or CART-19 cells (50% transduced) were infused I.V.. Dosing of αCD19-Fab-GCN4-CL1 (I.V.) began on the same day, q.d. 0.5 mg/kg. After 5 days of dosing (day 11) mice were injected with luciferin and imaged on an in vivo imaging system (IVIS), n=3 or 4, average radiance (p/s/cm^2/sr) plotted measured per mouse, and plotted mean ± SEM, **p ≤ 0.05, one-way ANOVA. The difference between no treatment and swi-CAR-T + WT Fab is not statistically significant. Results are shown in FIG. **7**A.

Example 13. Cloning, Expression and Purification of Anti-BCMA-IgG-GCN4$_{CL1}$

[0209] Cloning: Mammalian expression vector of CD19 IgG heavy chain was generated by in-frame ligation of amplified anti-BCMA IgG heavy chain (VH and CH1) to pFuse-hIgG1-Fc backbone vector (InvivoGen, CA). A gene encoding antibody BCMA light chain was amplified and cloned into the pFuse vector without hIgG1 Fc fragment. A gene encoding GCN4 (NYHLENEVARLKKL = SEQ ID NO: 3) with GGGGS (SEQ ID NO: 40, wherein n=1) linker at both ends was synthesized as oligonucleotides. Subsequently, anti-BCMA-IgG-GCN4$_{CL1}$ fusion proteins were created by grafting GCN4 with linker sequences at both ends into the CL region of the anti-BCMA light chain. The resulting mammalian expression vectors were confirmed by DNA sequencing.

[0210] Expression and Purification: anti-BCMA-IgG-GCN4$_{CL1}$ was expressed through transient transfection of FreeStyle HEK 293 cells with expression vectors of BCMA-IgG heavy chain and GCN4-BCMA-CL1 light chain, according to the manufacturer's protocol. Briefly, 28 mL FreeStyle HEK 293 cells containing 3×10^7 cells were seeded in a 125 mL shaking flask. 15 μg light chain plasmid and 15 μg heavy chain plasmid diluted in 1 mL Opti-MEM medium were added in 1 mL Opti-MEM containing 60 μL 293fectin (Invitrogen, Inc). After the plasmids were incubated with 293fectin for 30 min, the lipoplex mixture was added to the cell suspension. Cells were then shaken at 125 rpm in a 5% CO_2 environment at 37° C. Culture medium containing secreted proteins was harvested at 48 and 96 hours after transfection. anti-BCMA-IgG-GCN4$_{CL1}$ was purified by Protein G chromatography (Thermo Fisher Scientific, IL).

Example 14. Cytotoxicity of Anti-BCMA-IgG-GCN4$_{CL1}$ CAR-EC Switch with GCN4 Grafted to the Light Chain of an Anti-BCMA Antibody or Antibody Fragment

[0211] The cytotoxic activity of the anti-BCMA-IgG-GCN4$_{CL1}$ CAR-EC switch was assessed with the human PBMCs transduced with LV-EF1a-GCN4(52SR4) to create CAR-T-GCN4 at E:T ratios of 10:1 and 24 hour incubation. Transduction efficiency of PBMCs was approximately 50%. Activities were assessed against OPM2 (BCMA$^+$), by quantifying lactate dehydrogenase due to cytolysis of target cells (FIG. **8**, Table 5).

TABLE 5

Cytotoxicity of anti-BCMA-IgG-GCN4$_{CL1}$ CAR-EC switch and anti-GCN4 CAR-T cell

anti-BCMA-IgG-GCN4$_{CL1}$ switch concentration [pM]	% cytotoxicity
10000.000	35.52758
1000.000	35.06853
100.000	41.44725
10.000	31.59707
1.000	5.575391
0.100	1.13803
0.010	0.812881

[0212] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention.

TABLE 6

Chimeric Antigen Receptor -Nucleotide Sequence

NAME	SEQ ID NO	SEQUENCE
LV-EF1a-GCN4 (52SR4) -BBZ	1	CAGGTGGCACTTTTCGGGGAAATGTGCGCGGAACCCCTATTTGTTTATTTTTCTAAATACATTCAAA TATGTATCCGCTCATGAGACAATAACCCTGATAAATGCTTCAATAATATTGAAAAAGGAAGAGTAT GAGTATTCAACATTTCCGTGTCGCCCTTATTCCCTTTTTTGCGGCATTTTGCCTTCCTGTTTTTGCT CACCCAGAAACGCTGGTGAAAGTAAAAGATGCTGAAGATCAGTTGGGTGCACGAGTGGGTTA CATCGAACTGGATCTCAACAGCGGTAAGATCCTTGAGAGTTTTCGCCCCGAAGAACGTTTTC CAATGATGAGCACTTTTAAAGTTCTGCTATGT GGCGCGGTATTATCCCGTATTGACGCCGGGCAAGAGCAACTCGGTCGCCGCATACACTATTCTCA GAATGACTTGGTTGAGTACTCACCAGTCACAGAAAAGCATCTTACGGATGGCATGACAGTAAGA GAATTATGCAGTGCTGCCATAACCATGAGTGATAACACTGCGGCCAACTTACTTCTGACAAC GATCGGAGGACCGAAGGAGCTAACCGCTTTTTTGCACAACATGGGGGATCATGTAACTCGCCTT GATCGTTGGGAACCGGAGCTGAATGAAGCCATACCAAACGACGAGCGTGACACCACGATGCCTG

TABLE 6-continued

Chimeric Antigen Receptor -Nucleotide Sequence		
NAME	SEQ ID NO	SEQUENCE
		TAGCAATGGCAACAACGTTGCGCAAACTATTAACTGGCGAACTACTTACTCTAGCTTCCCGGCAA
		CAATTAATAGACTGGATGGAGGCGGATAAAGTTGCAGGACCACTTC
		TGCGCTCGGCCCTTCCGGCTGGCTGGTTTATTGCTGATAAATCTGGAGCCGGT
		GAGCGTGGGTCTCGCGGTATCATTGCAGCACTGGGGCCAGATGGTAAGCCCTCCCGTATCGTAGT
		TATCTACACGACGGGGAGTCAGGCAACTATGGATGAACGAAATAGACAGATCGCTGAGA
		TAGGTGCCTCACTGATTAAGCATTGGTAACTGTCAGACCAAGTTTACTCATATATACTTTAGATT
		GATTTAAAACTTCATTTTTAATTTAAAAGGATCTAGGTGAAGATCCTTTTTGATAATCTCATGAC
		CAAAATCCCTTAACGTGAGTTTTCGTTCCACTGAGCGTCAGACCCCGTAGAAAAGATCAAAG
		GATCTTCTTGAGATCCTTTTTTTCTGCGCGTAATCTGCTGCTTGCAAACAAAAAAACCACCGCTAC
		CAGCGGTGGTTTGTTTGCCGGATCAAGAGCTACCAACTCTTTTTCCGAAGGTAACTGGCTTCAG
		CAGAGCGCAGATACCAAATACTGTCCTTCTAGTGTAGCCGTAGTTAGGCCACCACTTCAA
		GAACTCTGTAGCACCGCCTACATACCTCGCTCTG
		CTAATCCTGTTACCAGTGGCTGCTGCCAGTGGCGATAAGTCGTGTCTTACCGGGTTGGACTCAA
		GACGATAGTTACCGGATAAGGCGCAGCGGTCGGGCTGAACGGGGGGTTCGTGCACACAGCC
		CAGCTTGGAGCGAACGACCTACACCGAACTGAGATACCTACAGCGTGAGCTATGAGAAAGCGC
		CACGCTTCCCGAAGGGAGAAAGGCGGACAGGTATCCGGTAAGCGGCAGGGTCGGAACAGGA
		GAGCGCACGAGGGAGCTTCCAGGGGGAAACGCCTGGTATCTTTATAGTCCTGTCGGGTTTCGC
		CACCTCTGACTTGAGCGTCGATTTTTGTGATGCTCGTCAGGGGGGCGGAGCCTATGGAAAAACGC
		CAGCAACGCGGCCTTTTTACGGTTCCTGGCCTTTTGCTGGCCTTTTGCTCA
		CATGTTCTTTCCTGCGTTATCCCCTGATTCTGTGGATAACCGTATTACCGCCTTTGAGTGAGCTGA
		TACCGCTCGCCGCAGCCGAACGACCGAGCGCAGCGAGTCAGTGAGCGAGGAAGCGGAA
		GAGCGCCCAATACGCAAACCGCCTCTCCCCGCGCGTTGGCCGATTCATTAATGCAGCTGGCACGA
		CAGGTTTCCCGACTGGAAAGCGGGC
		AGTGAGCGCAACGCAATTAATGTGAGTTAGCTCACTCATTAGGCACCCCAGGCTTTACACTT
		TATGCTTCCGGCTCGTATGTTGTGTGGAATTGTGAGCGGATAACAATTTCACACAGGAAACAGC
		TATGACCATGATTACGCCAAGCGCGCAATTAACCCTCACTAAAGGGAACAAAAGCTGGAGCTG
		CAAGCTTAATGTAGTCTTATGCAATACTCTTGTAGTCTTGCAACATGGTAACGATGAGTTAGCAA
		CATGCCTTACAAGGAGAGAAAAAGCACCGTGCATGCCGATTGGTGGAAGTAAGGTGGTAC
		GATCGTGCCTTATTAGGAAGGCAACAGACGGGTCTGACATGGATTGGACGAACCACT
		GAATTGCCGCATTGCAGAGATATTGTATTTAAGTGCCTAGCTCGATACAA
		TAAACGGGTCTCTCTGGTTAGACCAGATCTGAGCCTGGGAGCTCTCTGGCTAACTAGGGAACCC
		ACTGCTTAAGCCTCAATAAAGCTTGCCTTGAGTGCTTCAAGTAGTGTGTGCCCGTCTGTTGTGT
		GACTCTGGTAACTAGAGATCCCTCAGACCCTTTTAGTCAGTGTGGAAAATCTCTAG
		CAGTGGCGCCCGAACAGGGACCTGAAAGCGAAAGGGAAACCAGAGCTCTCTCGACGCAG
		GACTCGGCTTGCTGAAGCGCGCACGGCAAGAGGCGAGGGGCGGCGACTGGTGAGTACGC
		CAAAAATTTTGACTAGCGGAGGCTAGAAGGAGAGAGATGGGTGCGAGAGCGTCAGTAT
		TAAGCGGGGGAGAATTAGATCGCGATGGGAAAAAATTCGGTTAAGGCCAGGGGGAAAGAAAAAA
		TATAAATTAAAACATATAGTATGGGCAAGCAGGGAGCTAGAACGATTCGCAGT
		TAATCCTGGCCTGTTAGAAACATCAGAAGGCTGTAGACAAATACTGGGACAGCTACAAC
		CATCCCTTCAGACAGGATCAGAAGAACTTAGATCATTATATAATACAGTAGCAACCCTC
		TATTGTGTGCATCAAAGGATAGAGATAAAAGACACCAAGGAAGCTTTAGACAAGATAGAGGAA
		GAGCAAAACAAAAGTAAGACCACCGCACAGCAAGCGGCCGCTGATCTTCAGACCTGGAGGAG
		GAGATATGAGGGACAATTGGAGAAGTGAATTATATAAATATAAAGTAGTAAAAATTGAACCATTAG
		GAGTAGCACC
		CACCAAGGCAAAGAGAAGAGTGGTGCAGAGAGAAAAAAGAGCAGTGGGAATAG
		GAGCTTTGTTCCTTGGGTTCTTGGGAGCAGCAGGAAGCACTATGGGCGCAGCCTCAATGACGCT
		GACGGTACAGGCCAGACAATTATTGTCTGGTATAGTGCAGCAGCAGAACAATTTGCTGAGGGC
		TATTGAGGCGCAACAGCATCTGTTGCAACTCACAGTCTGGGGCATCAAGCAGCTCCAGGCAA
		GAATCCTGGCTGTGGAAAGATACCTAAAGGATCAACAGCTCCTGGGGATTTGGGGTTGCTCTG
		GAAAACTCATTTGCACCACTGCTGTGCCTTGGAATGCTAGTTGGAGTAATAAATCTCTGGAACA
		GATTGGAATCACACGACCTGGATGGAGTGGGACAGAGAAATTAACAATTACACAAGCTTAATA
		CACTCCTTAATTGAAGAATCGCAAAACCAGCAAGAAAAGAATGAACAAGAATTATTGGAATTAGA
		TAAATGGGCAAGTTTGTGGAATTGGTTTAACATAACAAATT
		GGCTGTGGTATATAAAATTATTCATAATGATAGTAGGAGGCTTGGTAGGTTTAAGAA
		TAGTTTTTGCTGTACTTTCTATAGTGAATAGAGTTAGGCAGGGATATTCACCATTATCGTTTCA
		GACCCACCTCCCAACCCCGAGGGGACCCGACAGGCCCGAAGGAATAGAAGAAGAAGGTGGAGA
		GAGAGACAGAGACAGATCCATTCGATTAGTGAACGGATCTCGACGGTTAACTTTTAAAA
		GAAAAGGGGGGATTGGGGGGTACAGTGCAGGGGAAAGAATAGTAGACATAATAGCAACAGACA
		TACAAACTAAAGAATTACAAAAACAAATTACAAAAATTCAAAATTTTATCGAGCTTTGCAAAGATG
		GATAAAGTTTTAAACAGAGAGGAATCTTTGCAGCTAATGGACCTTCTAGGTCTTGAAAG
		GAGTGCCTCGTGAGGCTCCGGTGCCCGTCAGTGGGCAGAGCGCACATCGCCCACAGTCCCCGA
		GAAGTTGGGGGGAGGGGTCGGCAATTGAACCGGTGCCTAGAGAAGGTGGCGCGGGG
		TAAACTGGGAAAGTGATGTCGTGTACTGGCTCCGCCTTTTTCCCGAGGGTGGGGGAGAACCGTA
		TATAAGTGCAGTAGTCGCCGTGAACGTTCTTTTTCGCAACGGGTTTGCCGCCAGAACACAGG
		TAAGTGCCGTGTGTGGTTCCCGCGGGCCTGGCCTCTTTACGGGTTATGGCCCTTGCGTGCCTT
		GAATTACTTCCA
		CCTGGCTGCAGTACGTGATTCTTGATCCCGAGCTTCGGGTTGGAAGTGGGTGGGAGAGTTC
		GAGGCCTTGCGCTTAAGGAGCCCCTTCGCCTCGTGCTTGAGTT
		GAGGCCTGGCCTGGGCGCTGGGGCCGCCGCGTGCGAATCTGGTGG
		CACCTTCGCGCCTGTCTCGCTGCTTTCGATAAGTCTCTAGCCATTTAAAATTTTTGAT
		GACCTGCTGCGACGCTTTTTTTCTGGCAAGATAGTCTTGTAAATGCGGGCCAAGATCTGCA
		CACTGGTATTTCGGTTTTTGGGGCCGCGGGCGGCGACGGGGCCCGTGCGTCCCAGCGCA
		CATGTTCGGCGAGGCGGGGCCTGCGAGCGCGGCCACCGAGAATCGGACGGGGGTAGTCT
		CAAGCTGGCCGGCCTGCTCTGGTGCCTGGCCTCGCGCCGCCGTGTATCGCCCCGCCCTGGGCGG
		CAAGGCTGGCCCGGTCGGCACCAGTTGCGTGAGCGGAAAGATGGCCGCTTCCCGGCCCTGCTG
		CAGGGAGCTCAAAATGGAGGACGCGGCGCTCGGGAGAGCGGGCGGGTGAGTCACCCACA
		CAAAGGAAAAGGGCCTTTCCGTCCTCAGCCGTCGCTTCATGT
		GACTCCACGGAGTACCGGGCGCCGTCCAGGCACCTCGATTAGTTCTCGAGCTTTTGGAG
		TACGTCGTCTTTAGGTTGGGGGGAGGGGTTTTATGCGATGGAGTTTCCCCACACTGAGTGGGTG
		GAGACTGAAGTTAGGCCAGCTTGGCACTTGATGTAATTCTCCTTGGAATTTGCCCTTTTT
		GAGTTTGGATCTTGGTTCATTCTCAAGCCTCAGACAGTGGTTCAAAGTTTTTTTCTTCCATTT
		CAGGTGTCGTGAGGAATTCGGTACCGCGGCCGCCCGGGGATCCATGGCCTTACCAGT
		GACCGCCTTGCTCCTGCCGCTGGCCTTGCTGCTCCACGCCGCCAGGCCGGACGCCGTTGTGACC
		CAGGAATCCGCTCTGACCTCTTCTCCAGGCGAAACCGTGACTCTGACTTGCCGTAGTAG
		CACCGGGGCTGTGACCACATCTAACTATGCCAGTTGGGTCCAGGAAAAACCGGATCACCTGTT
		TACTGGCCTGATTGGCGGCACCAACAATCGCGCACCGGGTGTGCCCGCTCGTTT

TABLE 6-continued

Chimeric Antigen Receptor -Nucleotide Sequence		
NAME	SEQ ID NO	SEQUENCE
		CAGCGGTTCCCTGATTGGGGACAAGGCAGCACTGACTATCACCGGCGCC
		CAGACCGAAGATGAGGCGATCTATTTTTGCGTCCTGTGGTACAGCGACCATTGGGTGTTCGGGG
		GAGGCACCAAACTGACAGTGCTGGGCGGAGGAGGAGGTTCAGGAGGAGGAGGTAGCGGGG
		GAGGCGGTTCCGGGGGAGGCGGTTCTGATGTGCAGCTGCAAGAATCCGGGCCAG
		GACTGGTTGCGCCTTCTCAGAGTCTGTCAATTACATGTACTGTTAGTGGCTTTCTGCTGACCGAC
		TATGGTGTGAACTGGGTTCGTCAGAGCCCAGGCAAGGGTCTGGAGTGGCTGGGAGT
		GATTTGGGGGGATGGAATCACAGACTACAATAGCGCACTGAAATCTCGGCTGAGTGTTACCAAA
		GATAACAGCAAGTCCCAGGTCTTCCTGAAGATGAACAGCCTGCAAAGCGGCGACTCCGCTCGC
		TATTACTGCGTTACCGGACTGTTTGATTATTGGGGGCAGGGGACAACTCTGACTGTTTCCTCCAC
		CACGACGCCAGCGCCGCGACCACCAACACCGGCGCCCACCATCGCGTCG
		CAGCCCCTGTCCCTGCGCCCAGAGGCGTGCCGGCCAGCGGCGGGGGGCGCAGTGCACAC
		GAGGGGGCTGGACTTCGCCTGTGATATCTACATCTGGGCGCCCTTGGCCGG
		GACTTGTGGGGTCCTTCTCCTGTCACTGGTTATCACCCTTTACT
		GCAAACGGGGCAGAAAGAAACTCCTGTATATATTCAAACAACCATTTATGAGACCAGTACAAAC
		TACTCAAGAGGAAGATGGCTGTAGCTGCCGATTTCCAGAAGAAGAAGAAGGAGGATGTGAACT
		GAGAGTGAAGTTCAGCAGGAGCGCAGACGCCCCCGCGTACAAGCAGGGCCAGAACCAGCTCTA
		TAACGAGCTCAATCTAGGACGAAGAGAGGAGTACGATGTTTTGGACAAGAGACGTGGCCGG
		GACCCTGAGATGGGGGGAAAGCCGAGAAGGAAGAACCCTCAGGAAGGCCTGTACAATGAACTG
		CAGAAAGATAAGATGGCGGAGGCCTACAGTGAGATTGGGATGAAAGGCGAGCGCCGGAGGGG
		CAAGGGGCACGATGGCCTTTACCAGGGTCTCAGTACAGCCACCAAGGACACCTACGACGCCCTT
		CACATGCAGGCCCTGCCCCCTCGCTAAGTCGACAATCAACCTCTGGATTACAAAATTTGTGAAA
		GATTGACTGGTATTCTTAACTATGTTGCTCCTTTTACGCTATGTGGATAC
		GCTGCTTTAATGCCTTTGTATCATGCTATTGCTTCCCGTATGGCTTTCATTTTCTCCTCCTTGTA
		TAAATCCTGGTTGCTGTCTCTTTATGAGGAGTTGTGGCCCGTTGTCAGGCAACGTGGCGTGGTGTG
		CACTGTGTTTGCTGACGCAACCCCCACTGGTTGGGGCATTGCCACCACCTGTCAGCTCCTTTCCGG
		GACTTTCGCTTTCCCCCTCCCTATTGCCACGGCGGAACTCATCGCCGCCTGCCTTGCCCGCTGCTG
		GACAGGGGCTCGGCTGTTGGGCACTGACAATTCCGTGGTGTTGTCGGGGAAGCTGACGTCCTTTC
		CATGGCTGCTCGCCTGTGTTGCCACCTGGATTCTGCGCGGGACGTCCTTCTGC
		TACGTCCCTTCGGCCCTCAATCCAGCG
		GACCTTCCTTCCCGCGGCCTGCTGCCGGCTCTGCGGCCTCTTCCGCGTCTTCGCCTTCGCCCTCA
		GACGAGTCGGATC
		TCCCTTTGGGCCGCCTCCCCGCCTGGAATTCGAGCTCGGTACCTTTAAGACCAATGACTTACAAGG
		CAGCTGTAGATCTTAGCCACTTTTTAAAAGAAAAGGGGGGACTGGAAGGGCTAATTCACTCC
		CAACGAAGACAAGATCTGCTTTTTGCTTGTACTGGGTCTCTCTGGTTAGACCAGATCTGAGCCTGG
		GAGCTCTCTGGCTAACTAGGGAACCCACTGCTTAAGCCTCAATAAAGCTTGCCTTGAGTGCTT
		CAAGTAGTGTGTGCCCGTCTGTTGTGTGACTCTGGTAACTAGAGATCCCTCAGACCCTTTTAGT
		CAGTGTGGAAAATCTCTAGCAGTAGTAGTTCATGTCATCTTATTATTCAGTATTTATAACTTGCAAA
		GAAATGAATATCAGAGAGTGAGAGGAACTTGTTTATTGCAGCTTATAATGGTTACAAATAAAGCAA
		TAGCATCACAAATTTCACAAATAAAGCATTTTTTTCACTGCATTCTAGTTGTGGTTTGT
		CCAAACTCATCAATGTATCTTATCATGTCTGGCTCTAGCTATCCCGCCCCTAACTCCGCC
		CAGTTCCGCCCATTCTCCGCCCCATGGCTGACTAATTTTTTTTATTTATGCAGAGGCC
		GAGGCCGCCTCGGCCTCTGAGCTATTCCAGAAGTAGTGAGGAGGCTTTTTTGGAGGCC
		TAGGCTTTTGCGTCGAGACGTACCCAATTCGCCCTATAGTGAGTCGTATTACGCGCGCT
		CACTGGCCGTCGTTTTACAACGTCGTGACTGGGAAAACCCTGGCGTTACCCAACTTAATCGCCTTG
		CAGCACATCCCCCTTTCGCCAGCTGGCGTAATAGCGAAGAGGCCCGCACCGATCGCCCTTCCCAA
		CAGTTGCGCAGCCTGAATGGCGAATGGCGCGACGCGCCCTGTAGCGGCGCAT
		TAAGCGCGGCGGGTGTGGTGGTTACGCGCAGCGTGACCGCTACACTTGCCAGCGCCC
		TAGCGCCCGCTCCTTTCGCTTTCTTCCCTTCCTTTCTCGCCACGTTCGCCGGCTTTCCCCGT
		CAAGCTCTAAATCGGGGGCTCCCTTTAGGGTTCCGATTTAGTGCTTTACGGCACCTCGACCC
		CAAAAAACTTGATTAGGGTGATGGTTCACGTAGTGGGCCATCGCCCTGATA
		GACGGTTTTTCGCCCTTTGACGTTGGAGTCCACGTTCTTTAATAGTGGACTCTTGTTCCAAACT
		GGAACAACACTCAACCCTATCTCGGTCTATTCTTTTGATTTATAAGGGATTTTGCCGATTTCGGCC
		TATTGGTTAAAAAATGAGCTGATTTAACAAAAATTTAACGCGAATTTTAACAAAATATTAACGTTTA
		CAATTTCC

TABLE 7

CAR Binding Region -Nucleotide & Amino Acid Sequences		
NAME	SEQ ID NO	SEQUENCE
yeast transcription factor GCN4 (7P14P)	2	RMKQLEPKVEELLPKNYHLENEVARLKKLVGER
yeast transcription factor GCN4 minimal binding peptide	3	NYHLENEVARLKKL
yeast transcription factor GCN4 minimal binding peptide with linkers	4	GGGGSNYHLENEVARLKKLGGGGS
Hydrophilic target peptide (HTP)	5	GGGGSDYKDDDDK
Hydrophilic target peptide (HTP) P	6	GGGGSDYKDDDDKP
FLAG®	7	DYKDDDDK

TABLE 8

CAR-T switch targeting polypeptides-Nucleotide Sequence

NAME	SEQ ID NO	SEQUENCE
Light chain of anti-CD19 antibody	8	GACATCCAGATGACACAGACTACATCCTCCCTGTCTGCCTCTCTGGGAGACAGAGTCACCAT CAGTTGCAGGGCAAGTCAGGACATTAGTAAATATTTAAATTGGTATCAGCAGAAACCAGATG GAACTGTTAAACTCCTGATCTACCATACATCAAGATTACACTCAGGAGTCCCATCAAGGTTCAGTGG CAGTGGGTCTGGAACAGATTATTCTCTCACCATTAGCAACCTGGAGCAAGAAGATATTGCCACT TACTTTTGCCAACAGGGTAATACGCTTCCGTACACGTTCGGAGGGGGGACCAAGCTTGAGAT CAAACGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTG GAACTGCCTCTGTCGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTG GAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAG GACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACA CAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGTCCTCGCCCGTCACAAAGAGCTTCAA CAGGGGAGAGTGT
Heavy chain of anti-CD19 antibody Fab	9	GAGGTGAAACTGCAGGAGTCAGGACCTGGCCTGGTGGCGCCCTCACAGAGCCTGTCCGTCACATG CACTGTCTCAGGGGTCTCATTACCCGACTATGGTGTAAGCTGGATTCGCCAGCCTCCAC GAAAGGGTCTGGAGTGGCTGGGAGTAATATGGGGTAGTGAAACCACATACTATAATTCAGCTCT CAAATCCAGACTGACCATCATCAAGGACAACTCCAAGAGCCAAGTTTTCTTAAAAATGAA CAGTCTGCAAACTGATGACACAGCCATTTACTACTGTGCCAAACATTATTACTACGGTGGTAGC TATGCTATGGACTACTGGGGCCAAGGAACCTCAGTCACCGTCTCCTCAGCCTCCACCAAGGGCC CATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCA CAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACT CAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTC TACTCCCTCAGCAGCGTGGTGACTGTGCCCTCTAGCAGCTTGGGCACCCAGACCTACATCTG CAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGT
Heavy chain of anti-CD19 IgG	10	GAGGTGAAACTGCAGGAGTCAGGACCTGGCCTGGTGGCGCCCTCACAGAGCCTGTCCGTCACATG CACTGTCTCAGGGGTCTCATTACCCGACTATGGTGTAAGCTGGATTCGCCAGCCTCCAC GAAAGGGTCTGGAGTGGCTGGGAGTAATATGGGGTAGTGAAACCACATACTATAATTCAGCTCT CAAATCCAGACTGACCATCATCAAGGACAACTCCAAGAGCCAAGTTTTCTTAAAAATGAA CAGTCTGCAAACTGATGACACAGCCATTTACTACTGTGCCAAACATTATTACTACGGTGGTAGC TATGCTATGGACTACTGGGGCCAAGGAA CCTCAGTCACCGTCTCCTCAGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTC CAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCC GAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCA CACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACTGTGCCCTC TAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTG GACAAGAAAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTC CAGTCGCCGGACCGTCA GTCTTCCTCTTCCCTCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCA CATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTG GACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACG TACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTG CAAGGTCTCCAACAAAGGCCTCCCAAGCTCCATCGAGAAAACCATCTCCAAAGCCAAAGGG CAGCCCCGAGAACCACAGGTGTACACCCTGCC TCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCC CAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGAC CACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAG CAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTA CACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA
Light chain of Trastuzumab (anti-Her2)	11	ATGAAAAAGAATATCGCATTTCTTCTTGCTAGCATGTTCGTTTTTTCTATTGCTACAAACGCA TACGCTGACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCAC CATCACTTGCCGGGCAAGTCAGGATGTGAATACCGCGGTCGCATGGTATCAGCAGAAACCAGG GAAAGCCCCTAAGCTCCTGATCTATTCTGCATCCTTCTTGTATAGTGGGGTCCCATCAAGGTT CAGTGGCAGTAGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTG CAACTTACTACTGTCAACAGCAT TACACTACCCCTCCGACGTTCGGCCAAGGTACCAAGCTTGAGATCAAACGAACTGTGGCTGCAC CATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTG GAACTGCCTCTGTCGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTG GAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAG GACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACA CAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGTCCTCGCCCGTCACAAAGAGCTTCAA CAGGGGAGAGTGT
Heavy chain of Trastuzumab (anti-Her2)	12	ATGAAAAAGAATATCGCATTTCTTCTTGCATCTATGTTCGTTTTTTCTATTGCTACAAACGCG TACGCTGAGGTGCAGCTGGTGGAGTCTGGAGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGA GACTCTCCTGTGCAGCCTCTGGGTTCAATATTAAGGACACTTACATCCACTGGGTCCGCCAGGCTC CAGGGAAGGGGCTGGAGTGGGTCGCACGTATTTATCCTACCAATGGTTACACACGCTACGCA GACTCCGTGAAGGGCCGATTCACCATCTCCGCAGACACTTCCAAGAACACGGCGTATCTTCAAAT GAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTTCGAGATGGGGCGGTGACGGCTTC TATGCCATGGACTACTGGGGCCAAGGAACCCTGGTCACCGTCTCCTCAGCCTCCACCAAGGGCC CATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCA CAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACT CAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTC TACTCCCTCAGCAGCGTGGTGACTGTGCCCTCTAGCAGCTTGGGCACCCAGACCTACATCTG CAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAG CCCAAATCTTGTGACAAAACTCACACA
Light Chain of Rituximab (anti-CD20)	13	ATGAAAAAGAATATCGCATTTCTTCTTGCTAGCATGTTCGTTTTTTCTATTGCTACAAACGCA TACGCTCAGATTGTGCTGAGCCAGAGCCCGGCGATTCTGAGCGCGAGCCCGGGCGAAAAAGTGAC CATGACCTGCCGCGCGAGCAGCAGCGTGAGCTATATTCATTGGTTTCAGCAGAAACCGGGCAG CAGCCCGAAACCGTGGATTTATGCGACCAGCAACCTGGCGAGCGGCGTGCCGGTGCGCTT TAGCGGCAGCGGCAGCGGCACCAGCTATAGCCTGACCATTAGCCGCGTGGAAGCGGAA GATGCGGCGACCTATTATTGCCAGCAGTGGACCAGCAACCCGCCGACCTTTGGCGGCGGCAC CAAGCTTGAGATCAAACGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAG CAGTTGAAATCTGGAACTGCCTCTGTCGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGC CAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAG CAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTAC GAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGTCCTCGCCCGTCACAAA

TABLE 8-continued

CAR-T switch targeting polypeptides-Nucleotide Sequence

NAME	SEQ ID NO	SEQUENCE
		GAGCTTCAACAGGGGAGAGTGT
Heavy Chain of Rituximab (anti-CD20)	14	ATGAAAAAGAATATCGCATTTCTTCTTGCATCTATGTTCGTTTTTTCTATTGCTACAAACGCG TACGCTCAGGTGCAGCTGCAGCAGCCGGGCGCGGAACTGGTGAAACCGGGCGCGAGCGT GAAAATGAGCTGCAAAGCGAGCGGCTATACCTTTACCAGCTATAACATGCATTGGGTGAAACA GACCCCGGGCCGCGGCCTGGAATGGATTGGCGCGATTTATCCGGGCAACGGCGATACCAGCTA TAACCAGAAATTTAAAGGCAAAGCGACCCTGACCGCGGATAAAAGCAGCAGCACCGCGTATATG CAGCTGAGCAGCCTGACCAGCGAAGATAGCGCGGTGTATTATTGCGCGCGCAGCACCTAT TATGGCGGCGATTGGTATTTTAACGTGTGGGGCGCGGGCACCACCGTGACCGTGAGCGCGGCGAG CACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCA CAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACT CAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTC TACTCCCTCAGCAGCGTGGTGACTGTGCCCTCTAGCAGCTTGGGCACCCAGACCTACATCTG CAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGA CAAAACTCACACA
Light chain of Clone C225 (anti-EGFR)	15	ATGAGGGTCCCCGCTCAGCTCCTGGGGCTCCTGCTGCTCTGGCTCCCAGGTGCACGATGTGA CATCCTGCTGACCCAGTCCCCCGTGATCCTGTCCGTGTCCCCTGGC GAGCGGGTGTCCTTCTCCTGCCGGGCCTCCCAGTCCATCGGCACCAACATCCACTGGTATCAG CAGCGGACCAACGGCTCCCCTCGGCTGCTGATCAAGTACGCCTCCGAGTCTATCTCCGG CATCCCTTCCCGGTTCTCCGGCTCCGGCTCTGGCACCGACTTCACCCTGTCCATCAACTCCGTG GAGTCCGAGGATATCGCCGACTACTACTGCCAGCAGAACAACAACTGGCCTAC CACCTTCGGCGCTGGAACCAAGCTGGAGCTGAAGCGTACGGTGGCTGCACCATCTGTCTT CATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAA TAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGG TAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAG CACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCAT CAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTGATGA
Heavy chain of Clone C225 (anti-EGFR)	16	ATGGGTTGGAGCCTCATCTTGCTCTTCCTTGTCGCTGTTGCTACGCGTGTCCACTCCCAGGTG CAGCTGAAGCAGTCCGGCCCTGGCCTGGTGCAGCCTTCCCAGTCCCTGTCCATCACCTG CACCGTGTCCGGCTTCTCCCTGACCAACTACGGCGTGCACTGGGTGCGCCAGTCCCCCGG CAAGGGCCTGGAGTGGCTGGGCGTGATCTGGTCCGGCGGCAACACCGACTACAACACCCCTTT CACCTCCCGGCTGTCCATCAACAAGGACAACTCCAAGTCCCAGGTGTTCTTCAAGAT GAACTCCCTGCAGTCCAACGACACCGCCATCTACTACTGCGCCAGAGCCCTGACCTACTATGAC TACGAGTTCGCCTACTGGGGCCAGGGCACCCTGGTGACCGTGTCCGCCGCTAGCACCAAGGGCC CATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCA CAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACT CAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTC TACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTG CAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGA CAAAACTCACACATGCCCACCGTGCCCA
Light chain of anti-CLL-1 antibody	17	GAGAACGTGCTCACCCAATCCCCCGCCATTATGTCCGCCTCCCCAGGCGAAAAGGTGACAAT GACCTGCAGGGCCAGCTCCAACGTGATCAGCTCTTACGTGCACTGGTACCAG CAACGGTCCGGCGCCTCCCCTAAGCTGTGGATCTATAGCACAAG CAACCTGGCTTCCGGCGTGCCTGCACGGTTCAGCGGAAGCGGAAGCGGAACAAGTTACTCCCT CACCATTTCTAGCGTTGAAGCCGAGGATGCCGCTACATACTATTGTCAACAGTACAGCGGA TACCCCCTGACCTTCGGAGCCGGCACAAAACTGGAGCTCAAGAGAGCAGCTGCAGCTCC CAGCGTGTTCATTTTTCCTCCCTCCGACGAACAACTGAAAAGCGGAA CAGCCTCTGTCGTTTGCCTGTTGAACAATTTCTACCCTAGGGAGGCCAAGGTCCAGTGGAAAGTG GATAACGCTCTGCAAAGCGGAAATTCTCAGGAAAGCGTTACCGAACAGGATTCTAAGGACTCTACA TACTCTCTGTCTAGCACACTCACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGC GAAGTCACCCATCAGGGCCTGTCCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT
Heavy chain of anti-CLL-1 antibody	18	GACATCCAGCTGCAGGAGAGCGGCCCCGGCCTGGTGAAGCCCAGCCAGAGCCTGAGCCTGACCTG CAGCGTGACCGGCTACAGCATCACCAGCGCCTATTACTGGAACTGGATCCGGCAGTTCCCCGGCAA CAAGCTGGAGTGGATGGGCTACATCAGCTACGACGGCCGGAACAACTACAACCCAAGCCTGAA GAACCGGATCAGCATCACCCGGGACACCAGCAAGAACCAGTTTTTCCTGAAGCTGAACAGCGT GACCACAGAGGACACCGCCACCTATTACTGCGCCAAGGAGGGAGACTACGACGTGGGCAACTAC TACGCCATGGACTACTGGGGCCAGGGCACCAGCGTGACCGTGTCTAGCGCCCGGACCAAGGGCCC CAGCGTGTTCCCCCTGGCCCCCAGCTCTAAGAGCACCAGCGGCG GAACCGCCGCTCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGAGCTGGAA CAGCGGCGCCCTGACCAGCGGCGTGCACACCTTCCCCGCCGTGCTGCAGAGCTCTGGCCTGTA CAGCCTGAGCAGCGTGGTTACCGTGCCCAGTTCTTCCCTGGGCACCCAGACCTACATCTGCAACGT GAACCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTGGAGCCCAAGAGCTGC
Light chain of anti-CD33 antibody	19	GATATTCAGATGACCCAGAGCCCGAGCAGCCTGAGCGCGAGCGTGGGCGATCGCGTGACCAT TACCTGCCGCGCGAGCGAAAGCGTGGATAACTATGGCATTAGCTTTATGAACTGGTTTCAGCA GAAACCGGGCAAAGCGCCGAAACTGCTGATTTATGCGGCGAGCAACCAGGGCAGCGGCGTGCC GAGCCGCTTTAGCGGCAGCGGCAGCGGCACCGATTTTACCCTGAACATTAGCAGCCTGCAGCCG GATGATTTTGCGACCTATTATTGCCAGCAGAGCAAAGAAGTGCCGTGGACCTTTGGCCAGGGCAC CAAAGTGGAAATTAAACGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAG CAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGC CAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAG CAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTAC GAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAA GAGCTTCAACAGGGGAGAGTGT
Heavy chain of anti-CD33 antibody	20	CAGGTGCAGCTGGTGCAGAGCGGCGCGGAAGTGAAAAAACCGGGCAGCAGCGTGAAAGT GAGCTGCAAAGCGAGCGGCTATACCTTTACCGATTATAACATGCATTGGGTGCGC CAGGCGCCGGGCCAGGGCCTGGAATGGATTGGCTATATTTATCCGTATAACGGCGGCACCGGCTA TAACCAGAAATTTAAAAGCAAAGCGACCATTACCGCGGATGAAAGCACCAACACCGCGTATATG GAACTGAGCAGCCTGCGCAGCGAAGATACCGCGGTGTATTATTGCGCGCGCGGCCCGGCGATG GATTATTGGGGCCAGGGCACCCTGGTGACCGTGAGCAGCGCCTCCACCAAGGGCC CATCGGTCTTCCCCCTGGCACCCTCCTCCTAGAGCACCTCTGGGGGCA CAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACT CAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTC TACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTG CAACGTGAATCACAAGCCCAGCAACACCAAGGTCGACAAGAAAGTTGAGCC CAAATCTTGTGGTGGCGGTCACCATCACCATCATCACCACCAC

TABLE 9

CAR-T switch targeting polypeptides -Amino Acid Sequence

NAME	SEQ ID NO	SEQUENCE
Light chain of wildtype anti-CS1 antibody	21	DIQMTQSPSSLSASVGDRVTITCKASQDVGIAVAWYQQKPGKVPKLLIY WASTRHTGVPDRFSGSGSGTDFTLTISSLQPEDVATYYCQQYSSYPYTFGQGTKLEIK
Heavy chain of wildtype anti-CS1 antibody Fab	22	EVQLVESGGGLVQPGGSLRLSCAASGFDFSRYWMSWVRQAPGKGLEWIGEINPDSSTI NYAPSLKDKFIISRDNAKNSLYLQMNSLRAEDTAVYYCARPDGNYWYFDVWGQGTLVTVS SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC
Light chain of anti-EGFRvIII antibody (Hu806) Fab	23	DIQMTQSPSSMSVSVGDRVTITCHSSQDINSNIGWLQQKPGKSFK GLIYHGTNLDDGVPSRFSGSGSGTDYTLTISSLQPEDFATYYCVQYAQFPWTFGGGTKLEIKRT VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
Heavy chain of anti-EGFRvIII antibody (Hu806) Fab	24	QLQESGPGLVKPSQTLSLTCTVSGYSISSDFAWNWIRQPPGKGLEWMGYISYSGNTRYQPSLKSRI TISRDTSKNQFFLKLNSVTAADTATYYCVTAGRGFPYWGQGTLVTVSSASTKGPSVF PLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC
Light chain of anti-BCMA antibody (BCMA98) Fab	25	DIQMTQSPSSLSASVGDRVTITCRANQGISNNLNWYQQKPGKAPK PLIYYTSNLQSGVPSRFSGSGSGTDYTLTISSLQPEDFATYYCQQFTSLPYTFGQGTKLEIKRT VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
Heavy chain of anti-BCMA antibody (BCMA98) Fab	26	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNFDMAWVRQAPGKGLVWVSSITTGGGD TYYADSVKGRFTISRDNAKSTLYLQMDSLRSEDTAVYYCVRHGYYDGYHLFDYWGQGTLVTVS SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC
Light Chain of anti-CD19 antibody	27	DIQMTQTTSSLSASLGDRVTISCRASQDISKYLNWYQQKPDGTVKL LIYHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIATYFCQQGNTLPYTFGGGTKLEIKRTVAAPSV FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLS KADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
Heavy Chain of anti-CD19 antibody IgG	28	EVKLQESGPGLVAPSQSLSVTCTVSGVSLPDYGVSWIRQPPRKGLEWLGVIWGSETTYYN SALKSRLTIIKDNSKSQVFLKMNSLQTDDTAIYYCAKHYYYGGSYAMDYWGQGTSVTVS SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPP VAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
Heavy Chain of anti-CD19 antibody Fab	29	EVKLQESGPGLVAPSQSLSVTCTVSGVSLPDYGVSWIRQPPRKGLEWLGVIWGSETTYYN SALKSRLTIIKDNSKSQVFLKMNSLQTDDTAIYYCAKHYYYGGSYAMDYWGQGTSVTVS SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC

TABLE 10

CAR-T switches-Amino Acid Sequence

NAME	SEQ ID NO	SEQUENCE
anti-CD19 Fab CL1-GCN4 switch Light Chain	30	DIQMTQTTSSLSASLGDRVTISCRASQDISKYLNWYQQKPDGTVKL LIYHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIATYFCQQGNTLPYTFGGGTKLEIKRT VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS**GGGGS NYHLENEVARLKKLGGGGS**DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
anti-CD19 IgG CL1-GCN4 switch Light Chain	31	DIQMTQTTSSLSASLGDRVTISCRASQDISKYLNWYQQKPDGTVKL LIYHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIATYFCQQGNTLPYTFGGGTKLEIKRT VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS**GGGGS NYHLENEVARLKKLGGGGS**DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
anti-CD19 Fab HC1-GCN4 switch Heavy Chain	32	EVKLQESGPGLVAPSQSLSVTCTVSGVSLPDYGVSWIRQPPRKGLEWLGVIWGSETTYYN SALKSRLTIIKDNSKSQVFLKMNSLQTDDTAIYYCAKHYYYGGSYAMDYWGQGTSVTVS SASTKGPSVFPLAPSS**NYHLENEVARLKKLS**GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF PAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC
anti-CD19 IgG HC1-GCN4 switch Heavy Chain	33	EVKLQESGPGLVAPSQSLSVTCTVSGVSLPDYGVSWIRQPPRKGLEWLGVIWGSETTYYN SALKSRLTIIKDNSKSQVFLKMNSLQTDDTAIYYCAKHYYYGGSYAMDYWGQGTSVTVS SASTKGPSVFPLAPSS**NYHLENEVARLKKLS**GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF PAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPP VAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
anti-CD19 Fab C term-GCN4 switch Heavy Chain	34	EVKLQESGPGLVAPSQSLSVTCTVSGVSLPDYGVSWIRQPPRKGLEWLGVIWGSETTYYN SALKSRLTIIKDNSKSQVFLKMNSLQTDDTAIYYCAKHYYYGGSYAMDYWGQGTSVTVS SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC**GGGGSNYHLENEVARLKKL**
anti-CD19 IgG hinge-GCN4 switch Heavy Chain	35	EVKLQESGPGLVAPSQSLSVTCTVSGVSLPDYGVSWIRQPPRKGLEWLGVIWGSETTYYN SALKSRLTIIKDNSKSQVFLKMNSLQTDDTAIYYCAKHYYYGGSYAMDYWGQGTSVTVS SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC**GGGGSNYHLENE VARLKKLGGS**DKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIS

TABLE 10-continued

CAR-T switches-Amino Acid Sequence

NAME	SEQ ID NO	SEQUENCE
		KAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
anti-CD19 Fab CL1 N-term Light Chain	36	**NYHLENEVARLKKLGGGGS**DIQMTQTTSSLSASLGDRVTISCRASQDISKYLN WYQQKPDGTVKLLIYHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIATYFCQQGNTL PYTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
anti-BCMA GCN4 CL1 light chain	37	DIQMTQSPSSLSASVGDRVTITCRANQGISNNLNWYQQKPGKAPK PLIYYTSNLQSGVPSRFSGSGSGTDYTLTISSLQPEDFATYYCQQFTSLPYTFGQGTKLEIKRT VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS**GGGGS** **NYHLENEVARLKKLGGGGS**DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
anti-BCMA heavy chain WT IgG	38	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNFDMAWVRQAPGKGLVWVSSITTGGGD TYYADSVKGRFTISRDNAKSTLYLQMDSLRSEDTAVYYCVRHGYYDGYHLFDYWGQGTLVTVS SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPP VAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Bold indicates grafted region (peptide and/or linker(s). Underline indicates peptide.

TABLE 11

pBAD vector with CAR-T targeting moiety - Nucleotide Sequence

NAME	SEQ ID NO	SEQUENCE
pBAD-CD19wt	39	AAGAAACCAATTGTCCATATTGCATCAGACATTGCCGTC ACTGCGTCTTTTACTGGCTCTTCTCGCTAACCAAACCGGT AACCCTGATTATTTGCACGGAGTCACACTTTGCTATGCCA TAGCATTTTTATCCATAAGATTAGCGGATCCTACCTGACG CTTTTTATCGCAACTCTCTACTGTTTCTCCATACCCGTTTT TTTGGGCTAGAAATAATTTTGTTTAACTTTAAGAAGGAGA ATACATCAACTAGTACGCAAGTTCACGTAAAAAGGGTAT CTAGAGGTTGAGGTGATTTTATGAAAAAGAATATCGCAT TTCTTCTTGCTAGCATGTTCGTTTTTTCTATTGCTACAAAC GCATACGCTGACATCCAGATGACACAGACTACATCCTCC CTGTCTGCCTCTCTGGGAGACAGAGTCACCATCAGTTGCA GGGCAAGTCAGGACATTAGTAAATATTTAAATTGGTATC AGCAGAAACCAGATGGAACTGTTAAACTCCTGATCTACC ATACATCAAGATTACACTCAGGAGTCCCATCAAGGTTCA GTGGCAGTGGGTCTGGAACAGATTATTCTCTCACCATTAG CAACCTGGAGCAAGAAGATATTGCCACTTACTTTTGCCA ACAGGGTAATACGCTTCCGTACACGTTCGGAGGGGGGAC CAAGCTTGAGATCAAACGAACTGTGGCTGCACCATCTGT CTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA ACTGCCTCTGTCGTGTGCCTGCTGAATAACTTCTATCCCA GAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCC AATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACA GCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGC TGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCT GCGAAGTCACCCATCAGGGCCTGTCCTCGCCCGTCACAA AGAGCTTCAACAGGGGAGAGTGTTAAGCTGGGGATCCTC TAGAGGTTGAGGTGATTTTATGAAAAAGAATATCGCATT TCTTCTTGCATCTATGTTCGTTTTTTCTATTGCTACAAACG CGTACGCTGAGGTGAAACTGCAGGAGTCAGGACCTGGCC TGGTGGCGCCCTCACAGAGCCTGTCCGTCACATGCACTGT CTCAGGGGTCTCATTACCCGACTATGGTGTAAGCTGGATT CGCCAGCCTCCACGAAAGGGTCTGGAGTGGCTGGGAGTA ATATGGGGTAGTGAAACCACATACTATAATTCAGCTCTC AAATCCAGACTGACCATCATCAAGGACAACTCCAAGAGC CAAGTTTTCTTAAAAATGAACAGTCTGCAAACTGATGAC ACAGCCATTTACTACTGTGCCAAACATTATTACTACGGTG GTAGCTATGCTATGGACTACTGGGGCCAAGGAACCTCAG TCACCGTCTCCTCAGCCTCCACCAAGGGCCCATCGGTCTT CCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCAC AGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGA ACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAG CGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGA CTCTACTCCCTCAGCAGCGTGGTGACTGTGCCCTCTAGCA GCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACA AGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCC AAATCTTGTGACAAAACTCACACATAATAAGTCGACCGA TGCCCTTGAGAGCCTTCAACCCAGTCAGCTCCTTCCGGTG GGCGCGGGGCATGACTATCGTCGCCGCACTTATGACTGT CTTCTTTATCATGCAACTCGTAGGACAGGTGCCAAACGGT CTCCAGCTTGGCTGTTTTGGCGGATGAGAGAAGATTTTCA GCCTGATACAGATTAAATCAGAACGCAGAAGCGGTCTGA TAAAACAGAATTTGCCTGGCGGCAGTAGCGCGGTGGTCC CACCTGACCCCATGCCGAACTCAGAAGTGAAACGCCGTA GCGCCGATGGTAGTGTGGGGTCTCCCCATGCGAGAGTAG GGAACTGCCAGGCATCAAATAAAACGAAAGGCTCAGTCG AAAGACTGGGCCTTTCGTTTTATCTGTTGTTTGTCGGTGA

TABLE 11-continued

pBAD vector with CAR-T targeting moiety - Nucleotide Sequence

NAME	SEQ ID NO	SEQUENCE
		ACGCTCTCCTGAGTAGGACAAATCCGCCGGGAGCGGATT
		TGAACGTTGCGAAGCAACGGCCCGGAGGGTGGCGGGCA
		GGACGCCCGCCATAAACTGCCAGGCATCAAATTAAGCAG
		AAGGCCATCCTGACGGATGGCCTTTTTGCGTTTCTACAAA
		CTCTTTTTGTTTATTTTTCTAAATACATTCAAATATGTATC
		CGCTCATGAGACAATAACCCTGATAAATGCTTCAATAAT
		ATTGAAAAAGGAAGAGTATGAGTATTCAACATTTCCGTG
		TCGCCCTTATTCCCTTTTTTGCGGCATTTTGCCTTCCTGTT
		TTTGCTCACCCAGAAACGCTGGTGAAAGTAAAAGATGCT
		GAAGATCAGTTGGGTGCACGAGTGGGTTACATCGAACTG
		GATCTCAACAGCGGTAAGATCCTTGAGAGTTTTCGCCCC
		GAAGAACGTTTTCCAATGATGAGCACTTTTAAAGTTCTGC
		TATGTGGCGCGGTATTATCCCGTGTTGACGCCGGGCAAG
		AGCAACTCGGTCGCCGCATACACTATTCTCAGAATGACTT
		GGTTGAGTACTCACCAGTCACAGAAAAGCATCTTACGGA
		TGGCATGACAGTAAGAGAATTATGCAGTGCTGCCATAAC
		CATGAGTGATAACACTGCGGCCAACTTACTTCTGACAAC
		GATCGGAGGACCGAAGGAGCTAACCGCTTTTTTGCACAA
		CATGGGGGATCATGTAACTCGCCTTGATCGTTGGGAACC
		GGAGCTGAATGAAGCCATACCAAACGACGAGCGTGACA
		CCACGATGCCTGTAGCAATGGCAACAACGTTGCGCAAAC
		TATTAACTGGCGAACTACTTACTCTAGCTTCCCGGCAACA
		ATTAATAGACTGGATGGAGGCGGATAAAGTTGCAGGACC
		ACTTCTGCGCTCGGCCCTTCCGGCTGGCTGGTTTATTGCT
		GATAAATCTGGAGCCGGTGAGCGTGGGTCTCGCGGTATC
		ATTGCAGCACTGGGGCCAGATGGTAAGCCCTCCCGTATC
		GTAGTTATCTACACGACGGGGAGTCAGGCAACTATGGAT
		GAACGAAATAGACAGATCGCTGAGATAGGTGCCTCACTG
		ATTAAGCATTGGTAACTGTCAGACCAAGTTTACTCATATA
		TACTTTAGATTGATTTAAAACTTCATTTTTAATTTAAAAG
		GATCTAGGTGAAGATCCTTTTTGATAATCTCATGACCAAA
		ATCCCTTAACGTGAGTTTTCGTTCCACTGAGCGTCAGACC
		CCGTAGAAAAGATCAAAGGATCTTCTTGAGATCCTTTTTT
		TCTGCGCGTAATCTGCTGCTTGCAAACAAAAAAACCACC
		GCTACCAGCGGTGGTTTGTTTGCCGGATCAAGAGCTACC
		AACTCTTTTTCCGAAGGTAACTGGCTTCAGCAGAGCGCA
		GATACCAAATACTGTCCTTCTAGTGTAGCCGTAGTTAGGC
		CACCACTTCAAGAACTCTGTAGCACCGCCTACATACCTCG
		CTCTGCTAATCCTGTTACCAGTGGCTGCTGCCAGTGGCGA
		TAAGTCGTGTCTTACCGGGTTGGACTCAAGACGATAGTT
		ACCGGATAAGGCGCAGCGGTCGGGCTGAACGGGGGGTTC
		GTGCACACAGCCCAGCTTGGAGCGAACGACCTACACCGA
		ACTGAGATACCTACAGCGTGAGCTATGAGAAAGCGCCAC
		GCTTCCCGAAGGGAGAAAGGCGGACAGGTATCCGGTAA
		GCGGCAGGGTCGGAACAGGAGAGCGCACGAGGGAGCTT
		CCAGGGGGAAACGCCTGGTATCTTTATAGTCCTGTCGGG
		TTTCGCCACCTCTGACTTGAGCGTCGATTTTTGTGATGCT
		CGTCAGGGGGGCGGAGCCTATGGAAAAACGCCAGCAAC
		GCGGCCTTTTTACGGTTCCTGGCCTTTTGCTGGCCTTTTGC
		TCACATGTTCTTTCCTGCGTTATCCCCTGATTCTGTGGATA
		ACCGTATTACCGCCTTTGAGTGAGCTGATACCGCTCGCCG
		CAGCCGAACGACCGAGCGCAGCGAGTCAGTGAGCGAGG
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		ATCTGTGCGGTATTTCACACCGCATATGGTGCACTCTCAG
		TACAATCTGCTCTGATGCCGCATAGTTAAGCCAGTATACA
		CTCCGCTATCGCTACGTGACTGGGTCATGGCTGCGCCCCG
		ACACCCGCCAACACCCGCTGACGCGCCCTGACGGGCTTG
		TCTGCTCCCGGCATCCGCTTACAGACAAGCTGTGACCGTC
		TCCGGGAGCTGCATGTGTCAGAGGTTTTCACCGTCATCAC
		CGAAACGCGCGAGGCAGCAGATCAATTCGCGCGCGAAG
		GCGAAGCGGCATGCATAATGTGCCTGTCAAATGGACGAA
		GCAGGGATTCTGCAAACCCTATGCTACTCCGTCAAGCCG
		TCAATTGTCTGATTCGTTACCAATTATGACAACTTGACGG
		CTACATCATTCACTTTTTCTTCACAACCGGCACGGAACTC
		GCTCGGGCTGGCCCCGGTGCATTTTTTAAATACCCGCGAG
		AAATAGAGTTGATCGTCAAAACCAACATTGCGACCGACG
		GTGGCGATAGGCATCCGGGTGGTGCTCAAAAGCAGCTTC
		GCCTGGCTGATACGTTGGTCCTCGCGCCAGCTTAAGACG
		CTAATCCCTAACTGCTGGCGGAAAAGATGTGACAGACGC
		GACGGCGACAAGCAAACATGCTGTGCGACGCTGGCGATA
		TCAAAATTGCTGTCTGCCAGGTGATCGCTGATGTACTGAC
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		ACTCGTTAATCGCTTCCATGCGCCGCAGTAACAATTGCTC
		AAGCAGATTTATCGCCAGCAGCTCCGAATAGCGCCCTTC
		CCCTTGCCCGGCGTTAATGATTTGCCCAAACAGGTCGCTG
		AAATGCGGCTGGTGCGCTTCATCCGGGCGAAAGAACCCC
		GTATTGGCAAATATTGACGGCCAGTTAAGCCATTCATGC
		CAGTAGGCGCGCGGACGAAAGTAAACCCACTGGTGATAC
		CATTCGCGAGCCTCCGGATGACGACCGTAGTGATGAATC
		TCTCCTGGCGGGAACAGCAAAATATCACCCGGTCGGCAA
		ACAAATTCTCGTCCCTGATTTTTCACCACCCCCTGACCGC
		GAATGGTGAGATTGAGAATATAACCTTTCATTCCCAGCG
		GTCGGTCGATAAAAAAATCGAGATAACCGTTGGCCTCAA
		TCGGCGTTAAACCCGCCACCAGATGGGCATTAAACGAGT
		ATCCCGGCAGCAGGGGATCATTTTGCGCTTCAGCCATACT TTTCATACTCCCGCCATTCAGAG

TABLE 12

Linker-Amino Acid Sequence		
NAME	SEQ ID NO	SEQUENCE
	40	$(GGGGS)_n$, n is at least 1
	41	$(GGGS)_n$, n is at least 1
	42	$(GGS)_n$, n is at least 1
	43	$(G_mS)_n$, n is at least 1, m is at least 1
	44	$(X_mS)_n$, n is at least 1, m is at least 1 and X is an amino acid

TABLE 12-continued

Linker-Amino Acid Sequence		
NAME	SEQ ID NO	SEQUENCE

Bold indicates grafted region (peptide and/or linker(s)). Underline indicates peptide.

SEQUENCE LISTING

Sequence total quantity: 49
SEQ ID NO: 1 moltype = DNA length = 8835
FEATURE Location/Qualifiers
misc_feature 1..8835
note = Description of Artificial Sequence: Synthetic polynucleotide
source 1..8835
mol_type = other DNA
organism = synthetic construct

SEQ ID NO: 1

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ggccgcctcg gcctctgagc tattccagaa gtagtgagga ggctttttg gaggcctagg  8160
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gccgtcgttt tacaacgtcg tgactgggaa aaccctggcg ttacccaact taatcgcctt  8280
gcagcacatc ccccttcgc cagctggcgt aatagcgaag aggcccgcac cgatcgccct  8340
tcccaacagt tgcgcagcct gaatggcgaa tggcgcgacg cgccctgtag cggcgcatta  8400
agcgcggcgg gtgtggtggt tacgcgcagc gtgaccgcta cacttgccag cgccctagcg  8460
cccgctcctt tcgctttctt cccttcctttt ctcgccacgt tcgccggctt tccccgtcaa  8520
gctctaaatc gggggctccc tttagggttc cgatttagtg ctttacggca cctcgacccc  8580
aaaaaacttg attagggtga tggttcacgt agtgggccat cgccctgata gacggttttt  8640
cgcccttga cgttggagtc cacgttcttt aatagtggac tcttgttcca aactggaaca  8700
acactcaacc ctatctcggt ctattctttt gatttataag ggattttgcc gatttcggcc  8760
tattggttaa aaaatgagct gatttaacaa aaatttaacg cgaattttaa caaaatatta  8820
acgtttacaa tttcc                                                   8835

SEQ ID NO: 2           moltype = AA  length = 33
FEATURE                Location/Qualifiers
REGION                 1..33
                       note = Description of Artificial Sequence: Synthetic
                        polypeptide
source                 1..33
                       mol_type = protein
                       organism = synthetic construct
SEQ ID NO: 2
RMKQLEPKVE ELLPKNYHLE NEVARLKKLV GER                               33

SEQ ID NO: 3           moltype = AA  length = 14
FEATURE                Location/Qualifiers
REGION                 1..14
                       note = Description of Artificial Sequence: Synthetic peptide
source                 1..14
                       mol_type = protein
                       organism = synthetic construct
SEQ ID NO: 3
NYHLENEVAR LKKL                                                    14

SEQ ID NO: 4           moltype = AA  length = 24
FEATURE                Location/Qualifiers
REGION                 1..24
                       note = Description of Artificial Sequence: Synthetic peptide
source                 1..24
                       mol_type = protein
                       organism = synthetic construct
SEQ ID NO: 4
GGGGSNYHLE NEVARLKKLG GGGS                                         24

SEQ ID NO: 5           moltype = AA  length = 13
FEATURE                Location/Qualifiers
REGION                 1..13
                       note = Description of Artificial Sequence: Synthetic peptide
source                 1..13
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                     mol_type = protein
                     organism = synthetic construct
SEQ ID NO: 5
GGGGSDYKDD DDK                                                    13

SEQ ID NO: 6         moltype = AA  length = 14
FEATURE              Location/Qualifiers
REGION               1..14
                     note = Description of Artificial Sequence: Synthetic peptide
source               1..14
                     mol_type = protein
                     organism = synthetic construct
SEQ ID NO: 6
GGGGSDYKDD DDKP                                                   14

SEQ ID NO: 7         moltype = AA  length = 8
FEATURE              Location/Qualifiers
REGION               1..8
                     note = Description of Artificial Sequence: Synthetic peptide
source               1..8
                     mol_type = protein
                     organism = synthetic construct
SEQ ID NO: 7
DYKDDDDK                                                          8

SEQ ID NO: 8         moltype = DNA  length = 642
FEATURE              Location/Qualifiers
misc_feature         1..642
                     note = Description of Artificial Sequence: Synthetic
                      polynucleotide
source               1..642
                     mol_type = other DNA
                     organism = synthetic construct
SEQ ID NO: 8
gacatccaga tgacacagac tacatcctcc ctgtctgcct ctctgggaga cagagtcacc  60
atcagttgca gggcaagtca ggacattagt aaatatttaa attggtatca gcagaaacca  120
gatggaactg ttaaactcct gatctaccat acatcaagat tacactcagg agtcccatca  180
aggttcagtg gcagtgggtc tggaacagat tattctctca ccattagcaa cctggagcaa  240
gaagatattg ccacttactt ttgccaacag ggtaatacgc ttccgtacac gttcggaggg  300
gggaccaagc ttgagatcaa acgaactgtg gctgcaccat ctgtcttcat cttcccgcca  360
tctgatgagc agttgaaatc tggaactgcc tctgtcgtgt gcctgctgaa taacttctat  420
cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag  480
gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg  540
ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc  600
ctgtcctcgc ccgtcacaaa gagcttcaac aggggagagt gt                     642

SEQ ID NO: 9         moltype = DNA  length = 669
FEATURE              Location/Qualifiers
misc_feature         1..669
                     note = Description of Artificial Sequence: Synthetic
                      polynucleotide
source               1..669
                     mol_type = other DNA
                     organism = synthetic construct
SEQ ID NO: 9
gaggtgaaac tgcaggagtc aggacctggc ctggtggcgc cctcacagag cctgtccgtc  60
acatgcactg tctcaggggt ctcattaccc gactatggtg taagctggat tcgccagcct  120
ccacgaaagg gtctggagtg gctgggagta atatggggta gtgaaaccac atactataat  180
tcagctctca aatccagact gaccatcatc aaggacaact ccaagagcca agttttctta  240
aaaatgaaca gtctgcaaac tgatgacaca gccatttact actgtgccaa acattattac  300
tacggtggta gctatgctat ggactactgg ggccaaggaa cctcagtcac cgtctcctca  360
gcctccacca agggcccatc ggtcttcccc ctggcaccct cctccaagag cacctctggg  420
ggcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg  480
tggaactcag gcgccctgac cagcggcgtg cacaccttcc cggctgtcct acagtcctca  540
ggactctact ccctcagcag cgtggtgact gtgccctcta gcagcttggg cacccagacc  600
tacatctgca acgtgaatca caagcccagc aacaccaagg tggacaagaa agttgagccc  660
aaatcttgt                                                         669

SEQ ID NO: 10        moltype = DNA  length = 1347
FEATURE              Location/Qualifiers
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misc_feature 1..1347
note = Description of Artificial Sequence: Synthetic polynucleotide
source 1..1347
mol_type = other DNA
organism = synthetic construct

SEQ ID NO: 10
gaggtgaaac tgcaggagtc aggacctggc ctggtggcgc cctcacagag cctgtccgtc 60
acatgcactg tctcaggggt ctcattaccc gactatggtg taagctggat tcgccagcct 120
ccacgaaagg gtctggagtg gctgggagta atatggggta gtgaaaccac atactataat 180
tcagctctca aatccagact gaccatcatc aaggacaact ccaagagcca agttttctta 240
aaaatgaaca gtctgcaaac tgatgacaca gccatttact actgtgccaa acattattac 300
tacggtggta gctatgctat ggactactgg ggccaaggaa cctcagtcac cgtctcctca 360
gcctccacca agggcccatc ggtcttcccc ctggcaccct cctccaagag cacctctggg 420
ggcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg 480
tggaactcag gcgccctgac cagcggcgtg cacaccttcc cggctgtcct acagtcctca 540
ggactctact ccctcagcag cgtggtgact gtgccctcta gcagcttggg cacccagacc 600
tacatctgca acgtgaatca caagcccagc aacaccaagg tggacaagaa agttgagccc 660
aaatcttgtg acaaaactca cacatgccca ccgtgcccag cacctccagt cgccggaccg 720
tcagtcttcc tcttccctcc aaaacccaag gacaccctca tgatctcccg gacccctgag 780
gtcacatgcg tggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 840
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacaacagc 900
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag 960
tacaagtgca aggtctccaa caaaggcctc ccaagctcca tcgagaaaac catctccaaa 1020
gccaaagggc agccccgaga accacaggtg tacaccctgc ctccatcccg ggatgagctg 1080
accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctatcccag cgacatcgcc 1140
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg 1200
gactccgacg gctccttctt cctctacagc aagctcaccg tggacaagag caggtggcag 1260
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 1320
aagagcctct ccctgtctcc gggtaaa 1347

SEQ ID NO: 11 moltype = DNA length = 711
FEATURE Location/Qualifiers
misc_feature 1..711
note = Description of Artificial Sequence: Synthetic polynucleotide
source 1..711
mol_type = other DNA
organism = synthetic construct

SEQ ID NO: 11
atgaaaaaga atatcgcatt tcttcttgct agcatgttcg ttttttctat tgctacaaac 60
gcatacgctg acatccagat gacccagtct ccatcctccc tgtctgcatc tgtaggagac 120
agagtcacca tcacttgccg ggcaagtcag gatgtgaata ccgcggtcgc atggtatcag 180
cagaaaccag ggaaagcccc taagctcctg atctattctg catccttctt gtatagtggg 240
gtcccatcaa ggttcagtgg cagtagatct gggacagatt tcactctcac catcagcagt 300
ctgcaacctg aagattttgc aacttactac tgtcaacagc attacactac ccctccgacg 360
ttcggccaag gtaccaagct tgagatcaaa cgaactgtgg ctgcaccatc tgtcttcatc 420
ttcccgccat ctgatgagca gttgaaatct ggaactgcct ctgtcgtgtg cctgctgaat 480
aacttctatc ccagagaggc caaagtacag tggaaggtgg ataacgccct ccaatcgggt 540
aactcccagg agagtgtcac agagcaggac agcaaggaca gcacctacag cctcagcagc 600
accctgacgc tgagcaaagc agactacgag aaacacaaag tctacgcctg cgaagtcacc 660
catcagggcc tgtcctcgcc cgtcacaaag agcttcaaca ggggagagtg t 711

SEQ ID NO: 12 moltype = DNA length = 753
FEATURE Location/Qualifiers
misc_feature 1..753
note = Description of Artificial Sequence: Synthetic polynucleotide
source 1..753
mol_type = other DNA
organism = synthetic construct

SEQ ID NO: 12
atgaaaaaga atatcgcatt tcttcttgca tctatgttcg ttttttctat tgctacaaac 60
gcgtacgctg aggtgcagct ggtggagtct ggaggaggct tggtccagcc tgggggtcc 120
ctgagactct cctgtgcagc ctctgggttc aatattaagg acacttacat ccactgggtc 180
cgccaggctc cagggaaggg gctggagtgg gtcgcacgta tttatcctac caatggttac 240
acacgctacg cagactccgt gaagggccga ttcaccatct ccgcagacac ttccaagaac 300
acggcgtatc ttcaaatgaa cagcctgaga gccgaggaca cggccgtgta ttactgttcg 360
agatggggcg gtgacggctt ctatgccatg gactactggg gccaaggaac cctggtcacc 420
gtctcctcag cctccaccaa gggcccatcg gtcttccccc tggcaccctc ctccaagagc 480

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acctctgggg gcacagcggc cctgggctgc ctggtcaagg actacttccc cgaaccggtg  540
acggtgtcgt ggaactcagg cgccctgacc agcggcgtgc acaccttccc ggctgtccta  600
cagtcctcag gactctactc cctcagcagc gtggtgactg tgccctctag cagcttgggc  660
acccagacct acatctgcaa cgtgaatcac aagcccagca acaccaaggt ggacaagaaa  720
gttgagccca aatcttgtga caaaactcac aca                               753

SEQ ID NO: 13          moltype = DNA  length = 708
FEATURE                Location/Qualifiers
misc_feature           1..708
                       note = Description of Artificial Sequence: Synthetic
                        polynucleotide
source                 1..708
                       mol_type = other DNA
                       organism = synthetic construct
SEQ ID NO: 13
atgaaaaaga atatcgcatt tcttcttgct agcatgttcg ttttttctat tgctacaaac  60
gcatacgctc agattgtgct gagccagagc ccggcgattc tgagcgcgag cccgggcgaa  120
aaagtgacca tgacctgccg cgcgagcagc agcgtgagct atattcattg gtttcagcag  180
aaaccgggca gcagcccgaa accgtggatt tatgcgacca gcaacctggc gagcggcgtg  240
ccggtgcgct ttagcggcag cggcagcggc accagctata gcctgaccat tagccgcgtg  300
gaagcggaag atgcggcgac ctattattgc cagcagtgga ccagcaaccc gccgaccttt  360
ggcggcggca ccaagcttga gatcaaacga actgtggctg caccatctgt cttcatcttc  420
ccgccatctg atgagcagtt gaaatctgga actgcctctg tcgtgtgcct gctgaataac  480
ttctatccca gagaggccaa agtacagtgg aaggtggata acgccctcca atcgggtaac  540
tcccaggaga gtgtcacaga gcaggacagc aaggacagca cctacagcct cagcagcacc  600
ctgacgctga gcaaagcaga ctacgagaaa cacaaagtct acgcctgcga agtcacccat  660
cagggcctgt cctcgcccgt cacaaagagc ttcaacaggg gagagtgt               708

SEQ ID NO: 14          moltype = DNA  length = 756
FEATURE                Location/Qualifiers
misc_feature           1..756
                       note = Description of Artificial Sequence: Synthetic
                        polynucleotide
source                 1..756
                       mol_type = other DNA
                       organism = synthetic construct
SEQ ID NO: 14
atgaaaaaga atatcgcatt tcttcttgca tctatgttcg ttttttctat tgctacaaac  60
gcgtacgctc aggtgcagct gcagcagccg ggcgcggaac tggtgaaacc gggcgcgagc  120
gtgaaaatga gctgcaaagc gagcggctat acctttacca gctataacat gcattgggtg  180
aaacagaccc cgggccgcgg cctggaatgg attggcgcga tttatccggg caacggcgat  240
accagctata accagaaatt taaaggcaaa gcgaccctga ccgcggataa aagcagcagc  300
accgcgtata tgcagctgag cagcctgacc agcgaagata gcgcggtgta ttattgcgcg  360
cgcagcacct attatggcgg cgattggtat tttaacgtgt ggggcgcggg caccaccgtg  420
accgtgagcg cggcgagcac caagggccca tcggtcttcc ccctggcacc ctcctccaag  480
agcacctctg ggggcacagc ggccctgggc tgcctggtca aggactactt ccccgaaccg  540
gtgacggtgt cgtggaactc aggcgccctg accagcggcg tgcacacctt cccggctgtc  600
ctacagtcct caggactcta ctccctcagc agcgtggtga ctgtgccctc tagcagcttg  660
ggcacccaga cctacatctg caacgtgaat cacaagccca gcaacaccaa ggtggacaag  720
aaagttgagc ccaaatcttg tgacaaaact cacaca                            756

SEQ ID NO: 15          moltype = DNA  length = 708
FEATURE                Location/Qualifiers
misc_feature           1..708
                       note = Description of Artificial Sequence: Synthetic
                        polynucleotide
source                 1..708
                       mol_type = other DNA
                       organism = synthetic construct
SEQ ID NO: 15
atgagggtcc ccgctcagct cctggggctc ctgctgctct ggctcccagg tgcacgatgt  60
gacatcctgc tgacccagtc ccccgtgatc ctgtccgtgt cccctggcga gcgggtgtcc  120
ttctcctgcc gggcctccca gtccatcggc accaacatcc actggtatca gcagcggacc  180
aacggctccc ctcggctgct gatcaagtac gcctccgagt ctatctccgg catcccttcc  240
cggttctccg gctccggctc tggcaccgac ttcaccctgt ccatcaactc cgtggagtcc  300
gaggatatcg ccgactacta ctgccagcag aacaacaact ggcctaccac cttcggcgct  360
ggaaccaagc tggagctgaa gcgtacggtg gctgcaccat ctgtcttcat cttcccgcca  420
tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat  480
cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag  540
gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg  600
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ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc  660
ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gttgatga               708

SEQ ID NO: 16          moltype = DNA  length = 753
FEATURE                Location/Qualifiers
misc_feature           1..753
                       note = Description of Artificial Sequence: Synthetic
                        polynucleotide
source                 1..753
                       mol_type = other DNA
                       organism = synthetic construct
SEQ ID NO: 16
atgggttgga gcctcatctt gctcttcctt gtcgctgttg ctacgcgtgt ccactcccag  60
gtgcagctga agcagtccgg ccctggcctg gtgcagcctt cccagtccct gtccatcacc  120
tgcaccgtgt ccggcttctc cctgaccaac tacggcgtgc actgggtgcg ccagtccccc  180
ggcaagggcc tggagtggct gggcgtgatc tggtccggcg gcaacaccga ctacaacacc  240
cctttcacct cccggctgtc catcaacaag gacaactcca agtcccaggt gttcttcaag  300
atgaactccc tgcagtccaa cgacaccgcc atctactact gcgccagagc cctgacctac  360
tatgactacg agttcgccta ctggggccag ggcaccctgg tgaccgtgtc cgccgctagc  420
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gcggccctgg gctgcctggt caaggactac ttccccgaac cggtgacggt gtcgtggaac  540
tcaggcgccc tgaccagcgg cgtgcacacc ttcccggctg tcctacagtc ctcaggactc  600
tactccctca gcagcgtggt gaccgtgccc tccagcagct tgggcaccca gacctacatc  660
tgcaacgtga atcacaagcc cagcaacacc aaggtggaca agaaagttga gcccaaatct  720
tgtgacaaaa ctcacacatg cccaccgtgc cca                               753

SEQ ID NO: 17          moltype = DNA  length = 645
FEATURE                Location/Qualifiers
misc_feature           1..645
                       note = Description of Artificial Sequence: Synthetic
                        polynucleotide
source                 1..645
                       mol_type = other DNA
                       organism = synthetic construct
SEQ ID NO: 17
gagaacgtgc tcacccaatc ccccgccatt atgtccgcct ccccaggcga aaaggtgaca  60
atgacctgca gggccagctc caacgtgatc agctcttacg tgcactggta ccagcaacgg  120
tccggcgcct cccctaagct gtggatctat agcacaagca acctggcttc cggcgtgcct  180
gcacggttca gcggaagcgg aagcggaaca agttactccc tcaccatttc tagcgttgaa  240
gccgaggatg ccgctacata ctattgtcaa cagtacagcg gataccccct gaccttcgga  300
gccggcacaa aactggagct caagagagca gctgcagctc ccagcgtgtt catttttcct  360
ccctccgacg aacaactgaa aagcggaaca gcctctgtcg tttgcctgtt gaacaatttc  420
taccctaggg aggccaaggt ccagtggaaa gtggataacg ctctgcaaag cggaaattct  480
caggaaagcg ttaccgaaca ggattctaag gactctacat actctctgtc tagcacactc  540
acgctgagca aagcagacta cgagaaacac aaagtctacg cctgcgaagt cacccatcag  600
ggcctgtcct cgcccgtcac aaagagcttc aacaggggag agtgt                  645

SEQ ID NO: 18          moltype = DNA  length = 678
FEATURE                Location/Qualifiers
misc_feature           1..678
                       note = Description of Artificial Sequence: Synthetic
                        polynucleotide
source                 1..678
                       mol_type = other DNA
                       organism = synthetic construct
SEQ ID NO: 18
gacatccagc tgcaggagag cggccccggc ctggtgaagc ccagccagag cctgagcctg  60
acctgcagcg tgaccggcta cagcatcacc agcgcctatt actggaactg gatccggcag  120
ttccccggca acaagctgga gtggatgggc tacatcagct acgacggccg gaacaactac  180
aacccaagcc tgaagaaccg gatcagcatc acccgggaca ccagcaagaa ccagtttttc  240
ctgaagctga acagcgtgac cacagaggac accgccacct attactgcgc caaggaggga  300
gactacgacg tgggcaacta ctacgccatg gactactggg gccagggcac cagcgtgacc  360
gtgtctagcg cccggaccaa gggccccagc gtgttccccc tggcccccag ctctaagagc  420
accagcggcg gaaccgccgc tctgggctgc ctggtgaagg actacttccc cgagcccgtg  480
accgtgagct ggaacagcgg cgccctgacc agcggcgtgc acaccttccc cgccgtgctg  540
cagagctctg gcctgtacag cctgagcagc gtggttaccg tgcccagttc ttccctgggc  600
acccagacct acatctgcaa cgtgaaccac aagcccagca acaccaaggt ggacaagaaa  660
gtggagccca agagctgc                                                678

SEQ ID NO: 19          moltype = DNA  length = 654
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FEATURE               Location/Qualifiers
misc_feature          1..654
                      note = Description of Artificial Sequence: Synthetic
                       polynucleotide
source                1..654
                      mol_type = other DNA
                      organism = synthetic construct
SEQ ID NO: 19
gatattcaga tgacccagag cccgagcagc ctgagcgcga gcgtgggcga tcgcgtgacc  60
attacctgcc gcgcgagcga aagcgtggat aactatggca ttagctttat gaactggttt  120
cagcagaaac cgggcaaagc gccgaaactg ctgatttatg cggcgagcaa ccagggcagc  180
ggcgtgccga gccgctttag cggcagcggc agcggcaccg attttaccct gaacattagc  240
agcctgcagc cggatgattt tgcgacctat tattgccagc agagcaaaga agtgccgtgg  300
acctttggcc agggcaccaa agtggaaatt aaacgaactg tggctgcacc atctgtcttc  360
atcttcccgc catctgatga gcagttgaaa tctggaactg cctctgttgt gtgcctgctg  420
aataacttct atcccagaga ggccaaagta cagtggaagg tggataacgc cctccaatcg  480
ggtaactccc aggagagtgt cacagagcag gacagcaagg acagcaccta cagcctcagc  540
agcaccctga cgctgagcaa agcagactac gagaaacaca aagtctacgc ctgcgaagtc  600
acccatcagg gcctgagctc gcccgtcaca aagagcttca acaggggaga gtgt         654

SEQ ID NO: 20         moltype = DNA  length = 690
FEATURE               Location/Qualifiers
misc_feature          1..690
                      note = Description of Artificial Sequence: Synthetic
                       polynucleotide
source                1..690
                      mol_type = other DNA
                      organism = synthetic construct
SEQ ID NO: 20
caggtgcagc tggtgcagag cggcgcggaa gtgaaaaaac cgggcagcag cgtgaaagtg  60
agctgcaaag cgagcggcta tacctttacc gattataaca tgcattgggt gcgccaggcg  120
ccgggccagg gcctggaatg gattggctat atttatccgt ataacggcgg caccggctat  180
aaccagaaat ttaaaagcaa agcgaccatt accgcggatg aaagcaccaa caccgcgtat  240
atggaactga gcagcctgcg cagcgaagat accgcggtgt attattgcgc gcgcggccgc  300
ccggcgatgg attattgggg ccagggcacc ctggtgaccg tgagcagcgc ctccaccaag  360
ggcccatcgg tcttcccccc ggcaccctcc tcctagagca cctctggggg cacagcggcc  420
ctgggctgcc tggtcaagga ctacttcccc gaaccggtga cggtgtcgtg gaactcaggc  480
gccctgacca gcggcgtgca caccttcccg gctgtcctac agtcctcagg actctactcc  540
ctcagcagcg tggtgaccgt gccctccagc agcttgggca cccagaccta catctgcaac  600
gtgaatcaca agcccagcaa caccaaggtc gacaagaaag ttgagcccaa atcttgtggt  660
ggcggtcacc atcaccatca tcaccaccac                                   690

SEQ ID NO: 21         moltype = AA  length = 107
FEATURE               Location/Qualifiers
REGION                1..107
                      note = Description of Artificial Sequence: Synthetic
                       polypeptide
source                1..107
                      mol_type = protein
                      organism = synthetic construct
SEQ ID NO: 21
DIQMTQSPSS LSASVGDRVT ITCKASQDVG IAVAWYQQKP GKVPKLLIYW ASTRHTGVPD  60
RFSGSGSGTD FTLTISSLQP EDVATYYCQQ YSSYPYTFGQ GTKLEIK               107

SEQ ID NO: 22         moltype = AA  length = 222
FEATURE               Location/Qualifiers
REGION                1..222
                      note = Description of Artificial Sequence: Synthetic
                       polypeptide
source                1..222
                      mol_type = protein
                      organism = synthetic construct
SEQ ID NO: 22
EVQLVESGGG LVQPGGSLRL SCAASGFDFS RYWMSWVRQA PGKGLEWIGE INPDSSTINY  60
APSLKDKFII SRDNAKNSLY LQMNSLRAED TAVYYCARPD GNYWYFDVWG QGTLVTVSSA  120
STKGPSVFPL APSSKSTSGG TAALGCLVKD YFPEPVTVSW NSGALTSGVH TFPAVLQSSG  180
LYSLSSVVTV PSSSLGTQTY ICNVNHKPSN TKVDKKVEPK SC                     222

SEQ ID NO: 23         moltype = AA  length = 214
FEATURE               Location/Qualifiers
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REGION                  1..214
                        note = Description of Artificial Sequence: Synthetic
                         polypeptide
source                  1..214
                        mol_type = protein
                        organism = synthetic construct
SEQ ID NO: 23
DIQMTQSPSS MSVSVGDRVT ITCHSSQDIN SNIGWLQQKP GKSFKGLIYH GTNLDDGVPS  60
RFSGSGSGTD YTLTISSLQP EDFATYYCVQ YAQFPWTFGG GTKLEIKRTV AAPSVFIFPP  120
SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT  180
LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC                              214

SEQ ID NO: 24           moltype = AA  length = 217
FEATURE                 Location/Qualifiers
REGION                  1..217
                        note = Description of Artificial Sequence: Synthetic
                         polypeptide
source                  1..217
                        mol_type = protein
                        organism = synthetic construct
SEQ ID NO: 24
QLQESGPGLV KPSQTLSLTC TVSGYSISSD FAWNWIRQPP GKGLEWMGYI SYSGNTRYQP  60
SLKSRITISR DTSKNQFFLK LNSVTAADTA TYYCVTAGRG FPYWGQGTLV TVSSASTKGP  120
SVFPLAPSSK STSGGTAALG CLVKDYFPEP VTVSWNSGAL TSGVHTFPAV LQSSGLYSLS  180
SVVTVPSSSL GTQTYICNVN HKPSNTKVDK KVEPKSC                           217

SEQ ID NO: 25           moltype = AA  length = 214
FEATURE                 Location/Qualifiers
REGION                  1..214
                        note = Description of Artificial Sequence: Synthetic
                         polypeptide
source                  1..214
                        mol_type = protein
                        organism = synthetic construct
SEQ ID NO: 25
DIQMTQSPSS LSASVGDRVT ITCRANQGIS NNLNWYQQKP GKAPKPLIYY TSNLQSGVPS  60
RFSGSGSGTD YTLTISSLQP EDFATYYCQQ FTSLPYTFGQ GTKLEIKRTV AAPSVFIFPP  120
SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT  180
LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC                              214

SEQ ID NO: 26           moltype = AA  length = 224
FEATURE                 Location/Qualifiers
REGION                  1..224
                        note = Description of Artificial Sequence: Synthetic
                         polypeptide
source                  1..224
                        mol_type = protein
                        organism = synthetic construct
SEQ ID NO: 26
EVQLVESGGG LVQPGGSLRL SCAASGFTFS NFDMAWVRQA PGKGLVWVSS ITTGGGDTYY  60
ADSVKGRFTI SRDNAKSTLY LQMDSLRSED TAVYYCVRHG YYDGYHLFDY WGQGTLVTVS  120
SASTKGPSVF PLAPSSKSTS GGTAALGCLV KDYFPEPVTV SWNSGALTSG VHTFPAVLQS  180
SGLYSLSSVV TVPSSSLGTQ TYICNVNHKP SNTKVDKKVE PKSC                   224

SEQ ID NO: 27           moltype = AA  length = 214
FEATURE                 Location/Qualifiers
REGION                  1..214
                        note = Description of Artificial Sequence: Synthetic
                         polypeptide
source                  1..214
                        mol_type = protein
                        organism = synthetic construct
SEQ ID NO: 27
DIQMTQTTSS LSASLGDRVT ISCRASQDIS KYLNWYQQKP DGTVKLLIYH TSRLHSGVPS  60
RFSGSGSGTD YSLTISNLEQ EDIATYFCQQ GNTLPYTFGG GTKLEIKRTV AAPSVFIFPP  120
SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT  180
LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC                              214

SEQ ID NO: 28           moltype = AA  length = 449
FEATURE                 Location/Qualifiers
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REGION                  1..449
                        note = Description of Artificial Sequence: Synthetic
                         polypeptide
source                  1..449
                        mol_type = protein
                        organism = synthetic construct
SEQ ID NO: 28
EVKLQESGPG LVAPSQSLSV TCTVSGVSLP DYGVSWIRQP PRKGLEWLGV IWGSETTYYN  60
SALKSRLTII KDNSKSQVFL KMNSLQTDDT AIYYCAKHYY YGGSYAMDYW GQGTSVTVSS  120
ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS  180
GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPPVAGP  240
SVFLFPPKPK DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS  300
TYRVVSVLTV LHQDWLNGKE YKCKVSNKGL PSSIEKTISK AKGQPREPQV YTLPPSRDEL  360
TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ  420
QGNVFSCSVM HEALHNHYTQ KSLSLSPGK                                    449

SEQ ID NO: 29           moltype = AA  length = 223
FEATURE                 Location/Qualifiers
REGION                  1..223
                        note = Description of Artificial Sequence: Synthetic
                         polypeptide
source                  1..223
                        mol_type = protein
                        organism = synthetic construct
SEQ ID NO: 29
EVKLQESGPG LVAPSQSLSV TCTVSGVSLP DYGVSWIRQP PRKGLEWLGV IWGSETTYYN  60
SALKSRLTII KDNSKSQVFL KMNSLQTDDT AIYYCAKHYY YGGSYAMDYW GQGTSVTVSS  120
ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS  180
GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSC                    223

SEQ ID NO: 30           moltype = AA  length = 237
FEATURE                 Location/Qualifiers
REGION                  1..237
                        note = Description of Artificial Sequence: Synthetic
                         polypeptide
source                  1..237
                        mol_type = protein
                        organism = synthetic construct
SEQ ID NO: 30
DIQMTQTTSS LSASLGDRVT ISCRASQDIS KYLNWYQQKP DGTVKLLIYH TSRLHSGVPS  60
RFSGSGSGTD YSLTISNLEQ EDIATYFCQQ GNTLPYTFGG GTKLEIKRTV AAPSVFIFPP  120
SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSGG GGSNYHLENE  180
VARLKKLGGG GSDSTYSLSS TLTLSKADYE KHKVYACEVT HQGLSSPVTK SFNRGEC     237

SEQ ID NO: 31           moltype = AA  length = 237
FEATURE                 Location/Qualifiers
REGION                  1..237
                        note = Description of Artificial Sequence: Synthetic
                         polypeptide
source                  1..237
                        mol_type = protein
                        organism = synthetic construct
SEQ ID NO: 31
DIQMTQTTSS LSASLGDRVT ISCRASQDIS KYLNWYQQKP DGTVKLLIYH TSRLHSGVPS  60
RFSGSGSGTD YSLTISNLEQ EDIATYFCQQ GNTLPYTFGG GTKLEIKRTV AAPSVFIFPP  120
SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSGG GGSNYHLENE  180
VARLKKLGGG GSDSTYSLSS TLTLSKADYE KHKVYACEVT HQGLSSPVTK SFNRGEC     237

SEQ ID NO: 32           moltype = AA  length = 234
FEATURE                 Location/Qualifiers
REGION                  1..234
                        note = Description of Artificial Sequence: Synthetic
                         polypeptide
source                  1..234
                        mol_type = protein
                        organism = synthetic construct
SEQ ID NO: 32
EVKLQESGPG LVAPSQSLSV TCTVSGVSLP DYGVSWIRQP PRKGLEWLGV IWGSETTYYN  60
SALKSRLTII KDNSKSQVFL KMNSLQTDDT AIYYCAKHYY YGGSYAMDYW GQGTSVTVSS  120
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ASTKGPSVFP LAPSSNYHLE NEVARLKKLS GGTAALGCLV KDYFPEPVTV SWNSGALTSG  180
VHTFPAVLQS SGLYSLSSVV TVPSSSLGTQ TYICNVNHKP SNTKVDKKVE PKSC        234

SEQ ID NO: 33          moltype = AA  length = 460
FEATURE                Location/Qualifiers
REGION                 1..460
                       note = Description of Artificial Sequence: Synthetic
                        polypeptide
source                 1..460
                       mol_type = protein
                       organism = synthetic construct
SEQ ID NO: 33
EVKLQESGPG LVAPSQSLSV TCTVSGVSLP DYGVSWIRQP PRKGLEWLGV IWGSETTYYN  60
SALKSRLTII KDNSKSQVFL KMNSLQTDDT AIYYCAKHYY YGGSYAMDYW GQGTSVTVSS  120
ASTKGPSVFP LAPSSNYHLE NEVARLKKLS GGTAALGCLV KDYFPEPVTV SWNSGALTSG  180
VHTFPAVLQS SGLYSLSSVV TVPSSSLGTQ TYICNVNHKP SNTKVDKKVE PKSCDKTHTC  240
PPCPAPPVAG PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA  300
KTKPREEQYN STYRVVSVLT VLHQDWLNGK EYKCKVSNKG LPSSIEKTIS KAKGQPREPQ  360
VYTLPPSRDE LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY  420
SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPGK                        460

SEQ ID NO: 34          moltype = AA  length = 242
FEATURE                Location/Qualifiers
REGION                 1..242
                       note = Description of Artificial Sequence: Synthetic
                        polypeptide
source                 1..242
                       mol_type = protein
                       organism = synthetic construct
SEQ ID NO: 34
EVKLQESGPG LVAPSQSLSV TCTVSGVSLP DYGVSWIRQP PRKGLEWLGV IWGSETTYYN  60
SALKSRLTII KDNSKSQVFL KMNSLQTDDT AIYYCAKHYY YGGSYAMDYW GQGTSVTVSS  120
ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS  180
GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCGGGGSNY HLENEVARLK  240
KL                                                                 242

SEQ ID NO: 35          moltype = AA  length = 471
FEATURE                Location/Qualifiers
REGION                 1..471
                       note = Description of Artificial Sequence: Synthetic
                        polypeptide
source                 1..471
                       mol_type = protein
                       organism = synthetic construct
SEQ ID NO: 35
EVKLQESGPG LVAPSQSLSV TCTVSGVSLP DYGVSWIRQP PRKGLEWLGV IWGSETTYYN  60
SALKSRLTII KDNSKSQVFL KMNSLQTDDT AIYYCAKHYY YGGSYAMDYW GQGTSVTVSS  120
ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS  180
GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCGGGGSNY HLENEVARLK  240
KLGGSDKTHT CPPCPAPPVA GPSVFLFPPK PKDTLMISRT PEVTCVVVDV SHEDPEVKFN  300
WYVDGVEVHN AKTKPREEQY NSTYRVVSVL TVLHQDWLNG KEYKCKVSNK GLPSSIEKTI  360
SKAKGQPREP QVYTLPPSRD ELTKNQVSLT CLVKGFYPSD IAVEWESNGQ PENNYKTTPP  420
VLDSDGSFFL YSKLTVDKSR WQQGNVFSCS VMHEALHNHY TQKSLSLSPG K           471

SEQ ID NO: 36          moltype = AA  length = 233
FEATURE                Location/Qualifiers
REGION                 1..233
                       note = Description of Artificial Sequence: Synthetic
                        polypeptide
source                 1..233
                       mol_type = protein
                       organism = synthetic construct
SEQ ID NO: 36
NYHLENEVAR LKKLGGGGSD IQMTQTTSSL SASLGDRVTI SCRASQDISK YLNWYQQKPD  60
GTVKLLIYHT SRLHSGVPSR FSGSGSGTDY SLTISNLEQE DIATYFCQQG NTLPYTFGGG  120
TKLEIKRTVA APSVFIFPPS DEQLKSGTAS VVCLLNNFYP REAKVQWKVD NALQSGNSQE  180
SVTEQDSKDS TYSLSSTLTL SKADYEKHKV YACEVTHQGL SSPVTKSFNR GEC         233

SEQ ID NO: 37          moltype = AA  length = 237
FEATURE                Location/Qualifiers
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REGION                  1..237
                        note = Description of Artificial Sequence: Synthetic
                         polypeptide
source                  1..237
                        mol_type = protein
                        organism = synthetic construct
SEQ ID NO: 37
DIQMTQSPSS LSASVGDRVT ITCRANQGIS NNLNWYQQKP GKAPKPLIYY TSNLQSGVPS  60
RFSGSGSGTD YTLTISSLQP EDFATYYCQQ FTSLPYTFGQ GTKLEIKRTV AAPSVFIFPP  120
SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSGG GGSNYHLENE  180
VARLKKLGGG GSDSTYSLSS TLTLSKADYE KHKVYACEVT HQGLSSPVTK SFNRGEC     237

SEQ ID NO: 38           moltype = AA  length = 450
FEATURE                 Location/Qualifiers
REGION                  1..450
                        note = Description of Artificial Sequence: Synthetic
                         polypeptide
source                  1..450
                        mol_type = protein
                        organism = synthetic construct
SEQ ID NO: 38
EVQLVESGGG LVQPGGSLRL SCAASGFTFS NFDMAWVRQA PGKGLVWVSS ITTGGGDTYY  60
ADSVKGRFTI SRDNAKSTLY LQMDSLRSED TAVYYCVRHG YYDGYHLFDY WGQGTLVTVS  120
SASTKGPSVF PLAPSSKSTS GGTAALGCLV KDYFPEPVTV SWNSGALTSG VHTFPAVLQS  180
SGLYSLSSVV TVPSSSLGTQ TYICNVNHKP SNTKVDKKVE PKSCDKTHTC PPCPAPPVAG  240
PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN  300
STYRVVSVLT VLHQDWLNGK EYKCKVSNKG LPSSIEKTIS KAKGQPREPQ VYTLPPSRDE  360
LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW  420
QQGNVFSCSV MHEALHNHYT QKSLSLSPGK                                    450

SEQ ID NO: 39           moltype = DNA  length = 5574
FEATURE                 Location/Qualifiers
misc_feature            1..5574
                        note = Description of Artificial Sequence: Synthetic
                         polynucleotide
source                  1..5574
                        mol_type = other DNA
                        organism = synthetic construct
SEQ ID NO: 39
aagaaaccaa ttgtccatat tgcatcagac attgccgtca ctgcgtcttt tactggctct  60
tctcgctaac caaaccggta accctgatta tttgcacgga gtcacacttt gctatgccat  120
agcatttta tccataagat tagcggatcc tacctgacgc tttttatcgc aactctctac  180
tgtttctcca tacccgtttt tttgggctag aaataatttt gtttaacttt aagaaggaga  240
atacatcaac tagtacgcaa gttcacgtaa aaagggtatc tagaggttga ggtgatttta  300
tgaaaaagaa tatcgcattt cttcttgcta gcatgttcgt tttttctatt gctacaaacg  360
catacgctga catccagatg acacagacta catcctccct gtctgcctct ctgggagaca  420
gagtcaccat cagttgcagg gcaagtcagg acattagtaa atatttaaat tggtatcagc  480
agaaaccaga tggaactgtt aaactcctga tctaccatac atcaagatta cactcaggag  540
tcccatcaag gttcagtggc agtgggtctg gaacagatta ttctctcacc attagcaacc  600
tggagcaaga agatattgcc acttactttt gccaacaggg taatacgctt ccgtacacgt  660
tcggaggggg gaccaagctt gagatcaaac gaactgtggc tgcaccatct gtcttcatct  720
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agtaatatgg ggtagtgaaa ccacatacta taattcagct ctcaaatcca gactgaccat  1320
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cacagccatt tactactgtg ccaaacatta ttactacggt ggtagctatg ctatggacta  1440
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gactgtgccc tctagcagct tgggcaccca gacctacatc tgcaacgtga atcacaagcc  1740
cagcaacacc aaggtggaca agaaagttga gcccaaatct tgtgacaaaa ctcacacata  1800
ataagtcgac cgatgccctt gagagccttc aacccagtca gctccttccg gtgggcgcgg  1860
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ggcatgacta tcgtcgccgc acttatgact gtcttcttta tcatgcaact cgtaggacag  1920
gtgccaaacg gtctccagct tggctgtttt ggcggatgag agaagatttt cagcctgata  1980
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gcggtggtcc cacctgaccc catgccgaac tcagaagtga aacgccgtag cgccgatggt  2100
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cggtgcattt tttaaatacc cgcgagaaat agagttgatc gtcaaaacca acattgcgac  4800
cgacggtggc gataggcatc cgggtggtgc tcaaaagcag cttcgcctgg ctgatacgtt  4860
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gctccgaata gcgcccttcc ccttgcccgg cgttaatgat ttgcccaaac aggtcgctga  5160
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SEQ ID NO: 40          moltype = AA  length = 5
FEATURE                Location/Qualifiers
REGION                 1..5
                       note = Description of Artificial Sequence: Synthetic peptide
source                 1..5
                       mol_type = protein
                       organism = synthetic construct
```

-continued

```
SEQ ID NO: 40
GGGGS                                                          5

SEQ ID NO: 41          moltype = AA  length = 4
FEATURE                Location/Qualifiers
REGION                 1..4
                       note = Description of Artificial Sequence: Synthetic peptide
source                 1..4
                       mol_type = protein
                       organism = synthetic construct
SEQ ID NO: 41
GGGS                                                           4

SEQ ID NO: 42          moltype =   length =
SEQ ID NO: 42
000

SEQ ID NO: 43          moltype =   length =
SEQ ID NO: 43
000

SEQ ID NO: 44          moltype =   length =
SEQ ID NO: 44
000

SEQ ID NO: 45          moltype = AA  length = 25
FEATURE                Location/Qualifiers
REGION                 1..25
                       note = Description of Artificial Sequence: Synthetic peptide
REGION                 1..25
                       note = MISC_FEATURE - This sequence may encompass 1 to 5
                        "Gly Gly Gly Gly Ser" repeating units
source                 1..25
                       mol_type = protein
                       organism = synthetic construct
SEQ ID NO: 45
GGGGSGGGGS GGGGSGGGGS GGGGS                                    25

SEQ ID NO: 46          moltype = AA  length = 15
FEATURE                Location/Qualifiers
REGION                 1..15
                       note = Description of Artificial Sequence: Synthetic peptide
REGION                 1..15
                       note = MISC_FEATURE - This sequence may encompass 1 to 5
                        "Gly Gly Ser" repeating units
source                 1..15
                       mol_type = protein
                       organism = synthetic construct
SEQ ID NO: 46
GGSGGSGGSG GSGGS                                               15

SEQ ID NO: 47          moltype = AA  length = 5
FEATURE                Location/Qualifiers
REGION                 1..5
                       note = Description of Artificial Sequence: Synthetic peptide
source                 1..5
                       mol_type = protein
                       organism = synthetic construct
SEQ ID NO: 47
GSSSS                                                          5

SEQ ID NO: 48          moltype = AA  length = 5
FEATURE                Location/Qualifiers
REGION                 1..5
                       note = Description of Artificial Sequence: Synthetic peptide
source                 1..5
                       mol_type = protein
                       organism = synthetic construct
```

-continued

SEQ ID NO: 48
GGGGS 5

SEQ ID NO: 49 moltype = length =
SEQ ID NO: 49
000

What is claimed is:

1. A chimeric antigen receptor-effector cell switch comprising:

a. a peptidic antigen that binds a chimeric antigen receptor on an effector cell; and

b. a targeting moiety that binds a cell surface molecule on a target cell.

2. The chimeric antigen receptor-effector cell switch of claim **1**, wherein the peptidic antigen is based on or derived from a naturally occurring peptide.

3. The chimeric antigen receptor-effector cell switch of claim **2**, wherein the peptidic antigen is based on or derived from a non-human peptide.

4. The chimeric antigen receptor-effector cell switch of claim **2**, wherein the peptidic antigen is based on or derived from a eukaryotic peptide.

5. The chimeric antigen receptor-effector cell switch of claim **2**, wherein the peptidic antigen is based on or derived from a peptide, wherein the peptide is expressed by a yeast.

6. The chimeric antigen receptor-effector cell switch of claim **2**, wherein the peptidic antigen is based on or derived from a yeast transcription factor GCN4.

7. The chimeric antigen receptor-effector cell switch of claim **1**, wherein the peptidic antigen comprises a non-naturally occurring peptide.

8. The chimeric antigen receptor-effector cell switch of claim **7**, wherein the peptidic antigen comprises a synthetic peptide tag.

9. The chimeric antigen receptor-effector cell switch of claim **1**, wherein the peptidic antigen is based on or derived from a sequence selected from SEQ ID NOs: 2-7.

10. The chimeric antigen receptor-effector cell switch of claim **1**, wherein the peptidic antigen comprises a sequence that is at least about 50% homologous to a peptide sequence selected from SEQ ID NOs: 2-7.

11. The chimeric antigen receptor-effector cell switch of claim **1**, wherein the targeting moiety comprises a targeting peptide.

12. The chimeric antigen receptor-effector cell switch of claim **1**, wherein the targeting moiety comprises a targeting antibody or antibody fragment.

13. The chimeric antigen receptor-effector cell switch of claim **12**, wherein the targeting antibody or antibody fragment is selected from the group consisting of: an immunoglobulin, an Fc null immunoglobulin, and a Fab, and fragments thereof.

14. The chimeric antigen receptor-effector cell switch of claim **12**, wherein the targeting moiety is selected from the group consisting of: an anti-EGFR antibody, an anti-Her2 antibody, anti-EGFRvIII antibody, an anti-CD33 antibody, an anti-CLL-1 antibody, an anti-CEA antibody, an anti-CD19 antibody, an anti-CD22 antibody, an anti-BCMA antibody, and an anti-CS1 antibody, and fragments thereof.

15. The chimeric antigen receptor-effector cell switch of claim **12**, wherein the targeting antibody or antibody fragment comprises a light chain and a heavy chain pair, wherein the light chain and heavy chain are encoded by nucleic acid sequences based on or derived from nucleic acid sequence pairs selected from the group consisting of: SEQ ID NOs: 8 and 9; SEQ ID NOs: 8 and 10; SEQ ID NOs: 11 and 12; SEQ ID NOs. 13 and 14; SEQ ID NOs: 15 and 16; SEQ ID NOs: 17 and 18; and SEQ ID NOs: 19 and 20.

16. The chimeric antigen receptor-effector cell switch of claim **12**, wherein the targeting antibody or antibody fragment comprises a light chain and a heavy chain pair, wherein the light chain and heavy chain are encoded by amino acid sequences based on or derived from amino acid sequence pairs selected from the group consisting of: SEQ ID NOs: 21 and 22; SEQ ID NOs: 23 and 24; SEQ ID NOs. 25 and 26; SEQ ID NOs: 27 and 28; and SEQ ID NOs: 27 and 29.

17. The chimeric antigen receptor-effector cell switch of claim **12**, wherein the chimeric antigen receptor-effector cell switch comprises a light chain and a heavy chain pair, wherein the light chain and heavy chain are encoded by amino acid sequences based on or derived from amino acid sequence pairs selected from the group consisting of: SEQ ID NOs: 30 and 29; SEQ ID NOs: 36 and 29; SEQ ID NOs: 31 and 28; SEQ ID NOs: 27 and 32; SEQ ID NOs: 27 and 33; SEQ ID NOs: 27 and 34; and SEQ ID NOs: 27 and 35.

18. The chimeric antigen receptor-effector cell switch of claim **12**, wherein the peptidic antigen is fused to a terminus of the targeting antibody or antibody fragment.

19. The chimeric antigen receptor-effector cell switch of claim **12**, wherein the peptidic antigen is fused to a region of the targeting antibody or antibody fragment selected from the group consisting of: an N terminus of a light chain, a C terminus of a light chain, an N terminus of a heavy chain, a C terminus of a Fab heavy chain, and a C terminus of a constant region heavy chain.

20. The chimeric antigen receptor-effector cell switch of claim **1**, wherein the peptidic antigen is grafted into the targeting moiety.

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