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(54) **MODIFIED IMMUNE EFFECTOR CELL AND USE THEREOF**

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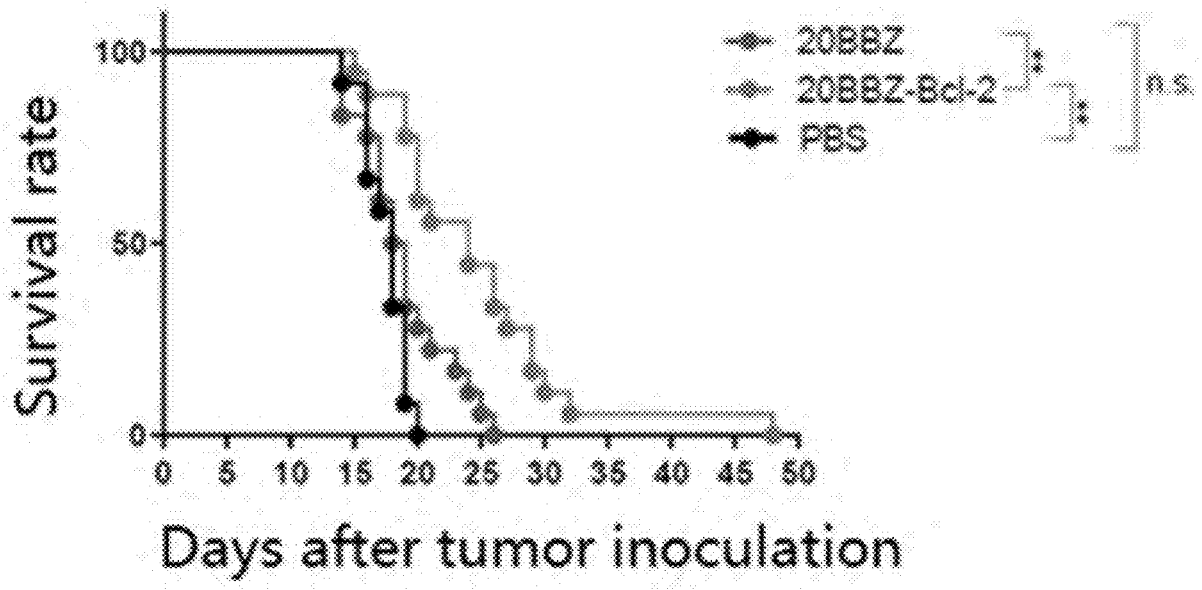
(57) **ABSTRACT**

An immune effector cell, including and/or expressing a chimeric antigen receptor (CAR), and a Bcl-2 protein or a functionally active fragment thereof. A composition including the immune effector cell. A method for treating diseases and/or disorders, including administering to a subject in need thereof the immune effector cell, where the diseases and/or disorders include tumors.

Specification includes a Sequence Listing.



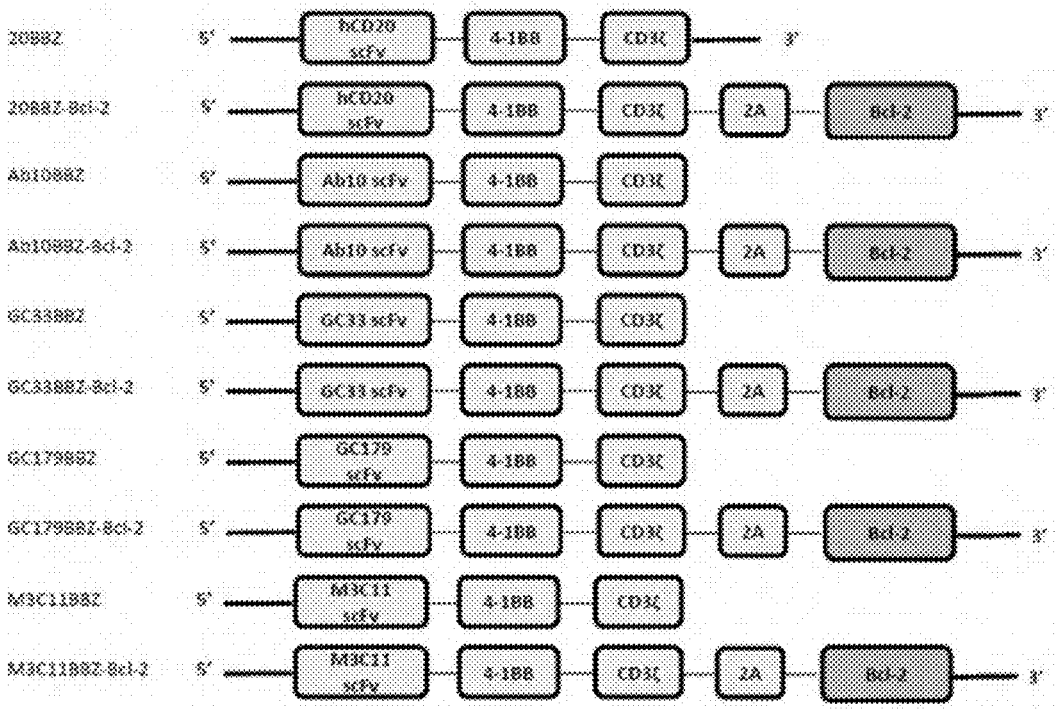

20BBZ
5'
hCD20 scFv
4-1BB
CD3ζ
3'
20BBZ-Bcl-2
2A
Bcl-2
Ab10BBZ
Ab10 scFv
Ab10BBZ-Bcl-2
GC33BBZ
GC33 scFv
GC33BBZ-Bcl-2
GC179BBZ
GC179 scFv
GC179BBZ-Bcl-2
M3C11BBZ
M3C11 scFv
M3C11BBZ-Bcl-2

Fig. 1

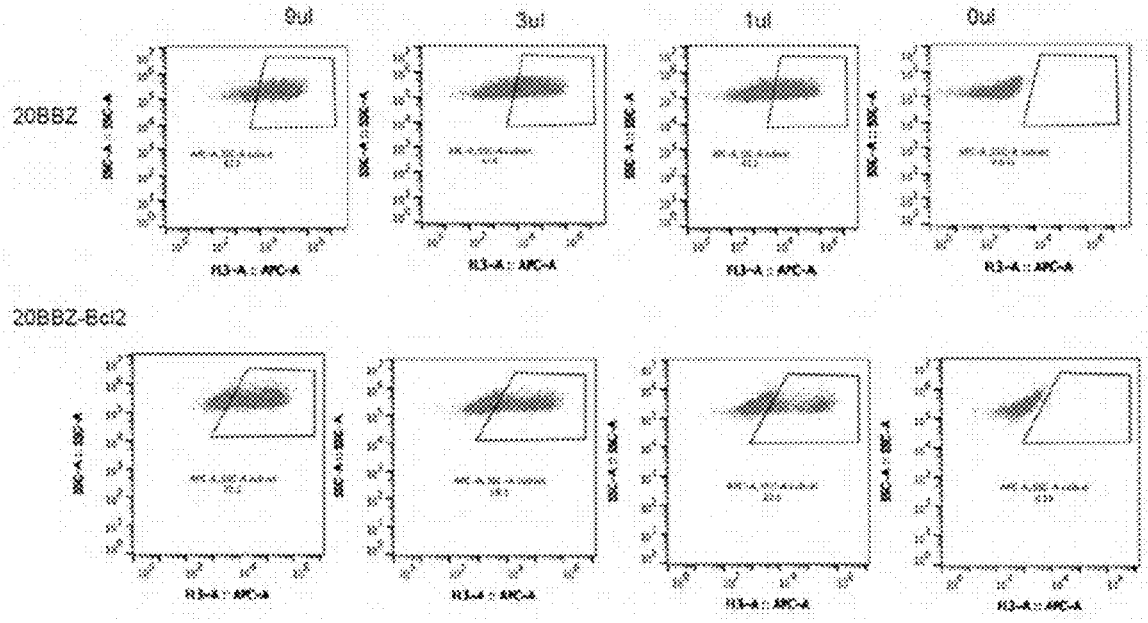

0ul
3ul
1ul
0ul
20BBZ
20BBZ-Bcl2

Fig. 2A

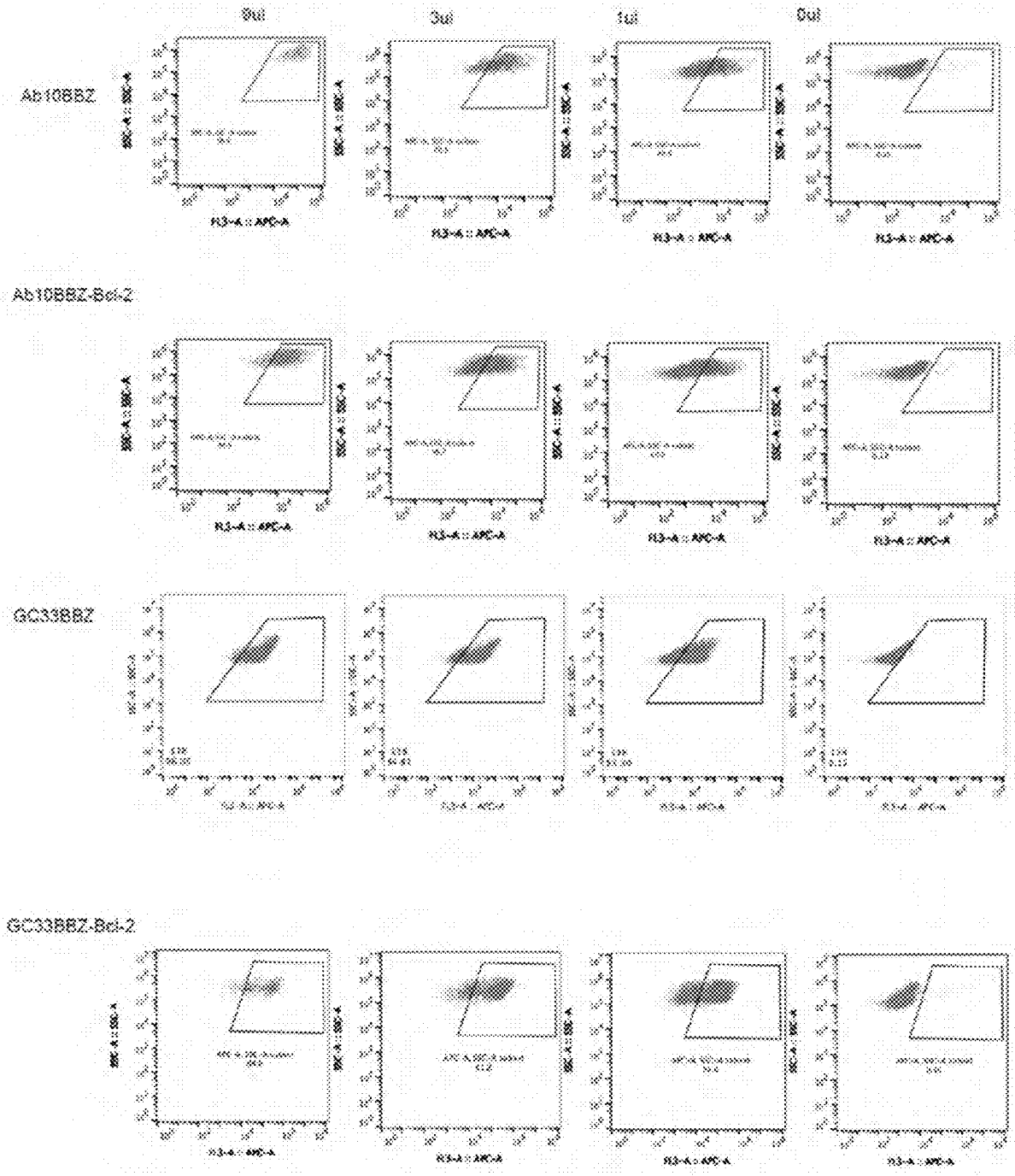


Fig. 2B

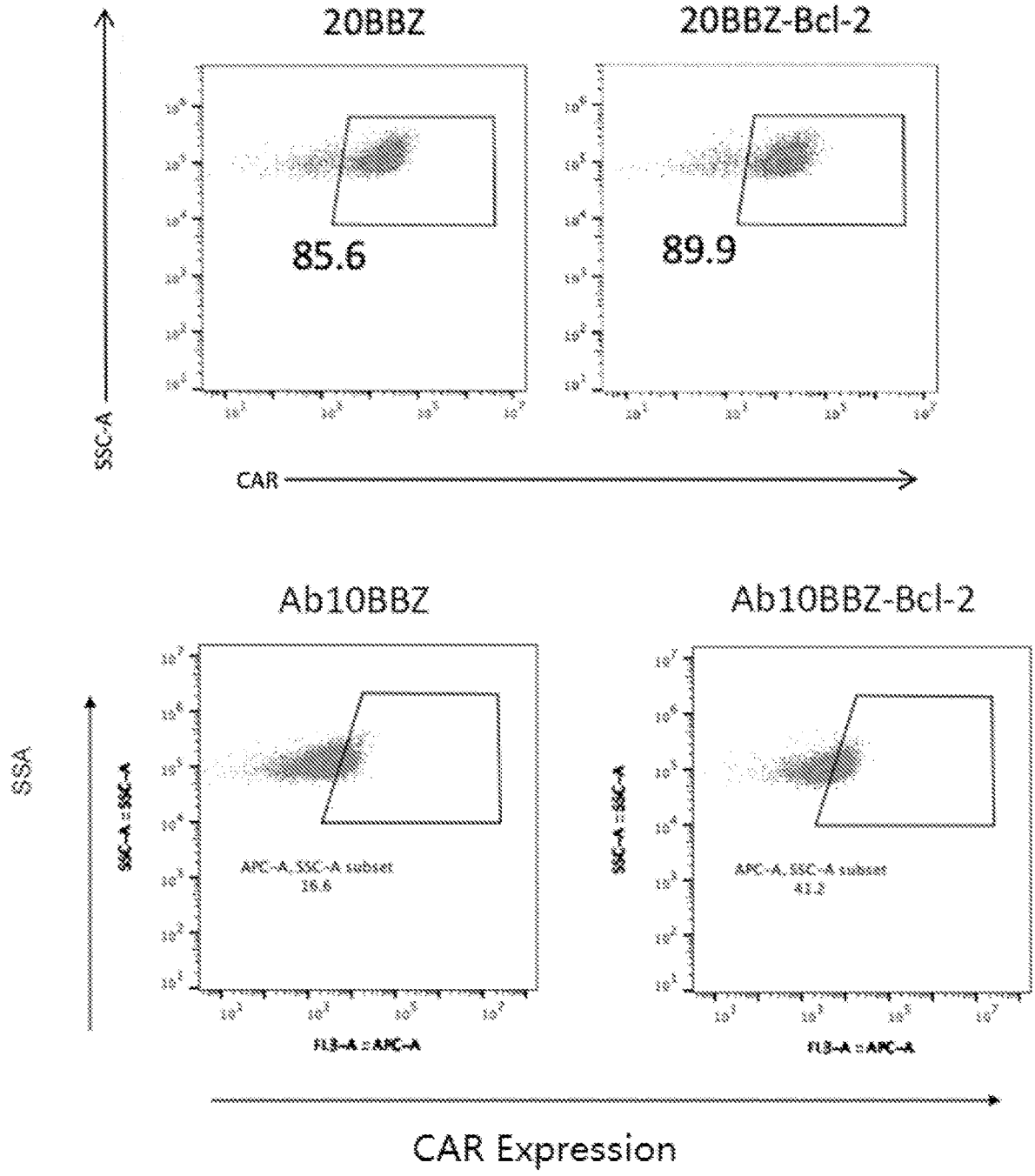

20BBZ
20BBZ-Bcl-2
85.6
89.9
SSC-A
CAR
Ab10BBZ
Ab10BBZ-Bcl-2
SSA
CAR Expression

Fig. 3

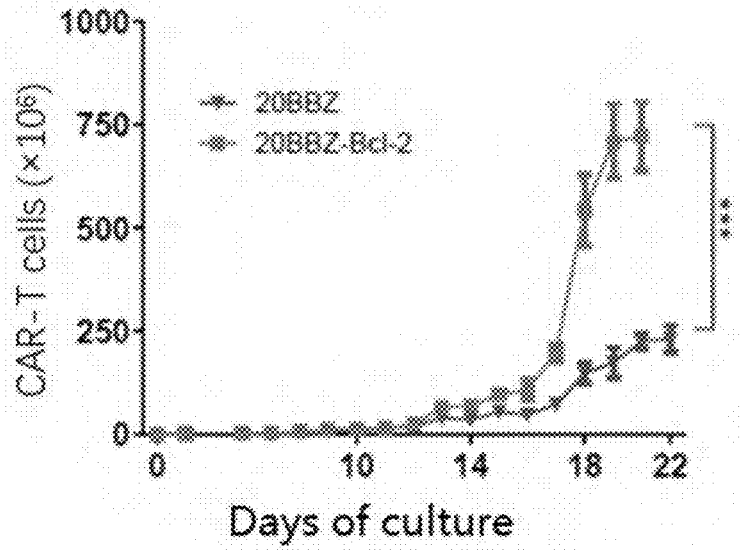

1000
750
500
250
0
CAR-T cells (×10⁶)
20BBZ
20BBZ-Bcl-2
***
0
10
14
18
22
Days of culture

Fig. 4

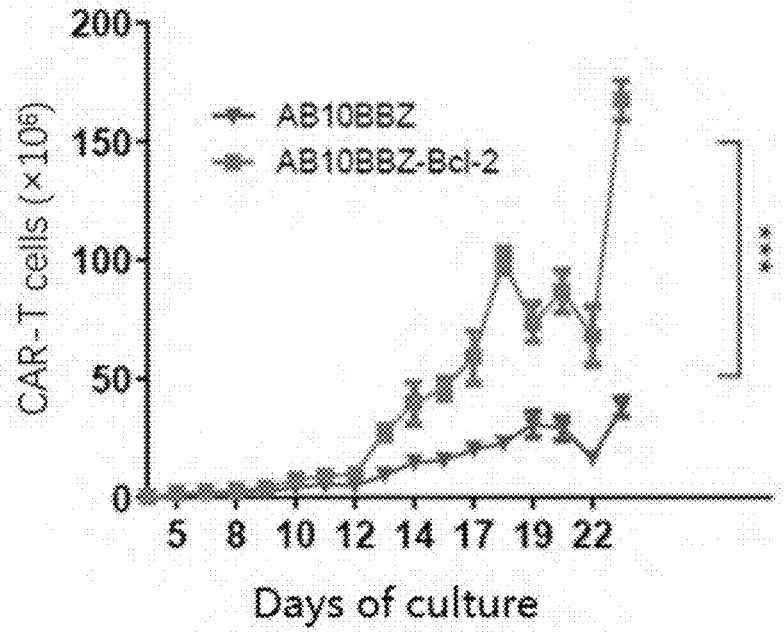

200
150
100
50
0
CAR-T cells (×10⁶)
AB10BBZ
AB10BBZ-Bcl-2
****
5 8 10 12 14 17 19 22
Days of culture

Fig. 5

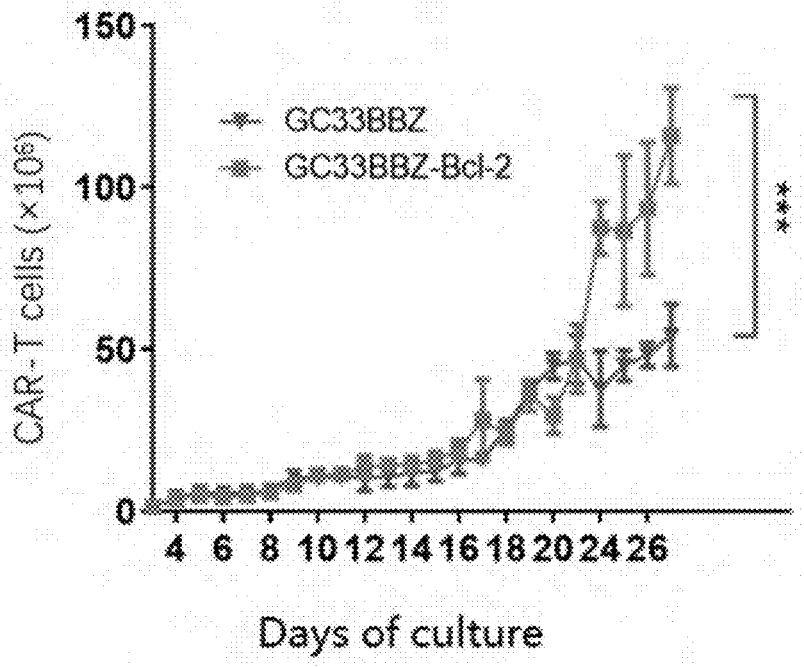

150
100
50
0
CAR-T cells (×10⁶)
GC33BBZ
GC33BBZ-Bcl-2
***
4 6 8 10 12 14 16 18 20 24 26
Days of culture

Fig. 6

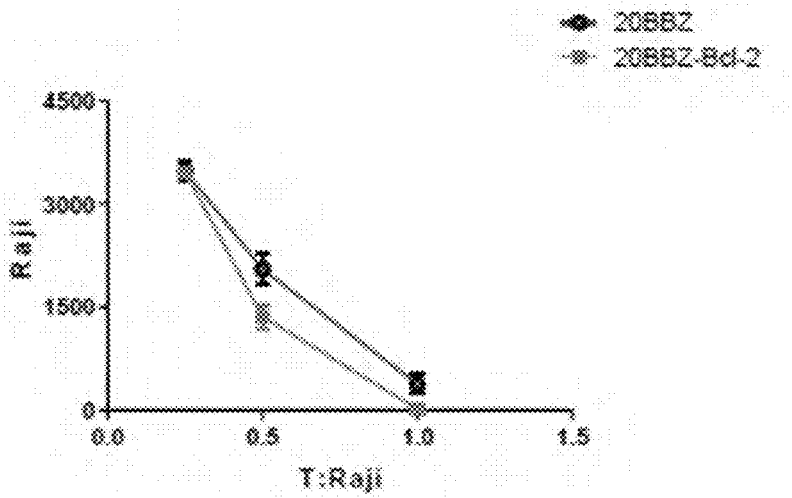
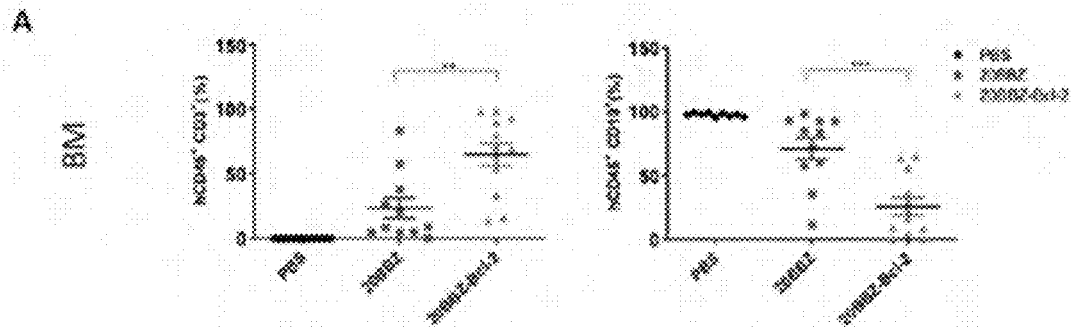

20BBZ
20BBZ-Bcl-2
4500
3000
1500
0
Raji
0.0
0.5
1.0
1.5
T:Raji

Fig. 7


A
BM
PBS
20BBZ
20BBZ-Bcl-2

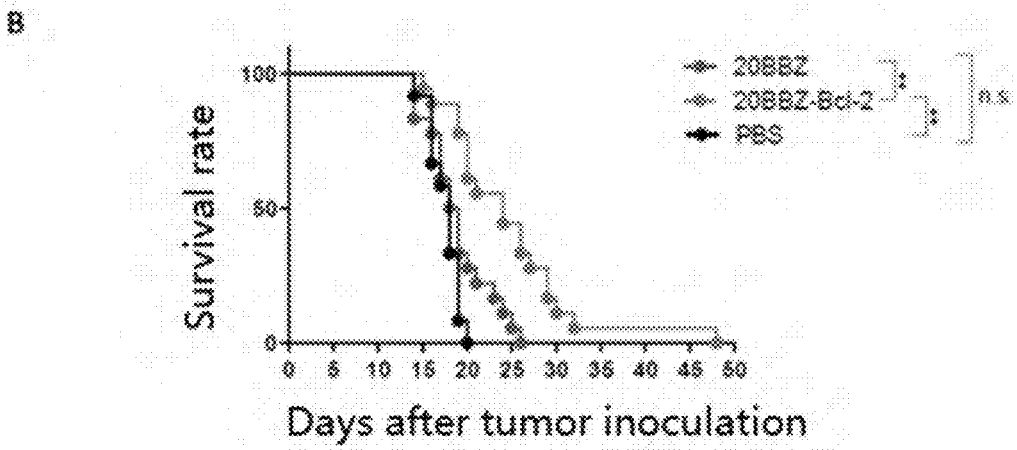

B
Survival rate
100
50
0
0 5 10 15 20 25 30 35 40 45 50
Days after tumor inoculation
20BBZ
20BBZ-Bcl-2
PBS
n.s

Fig. 8

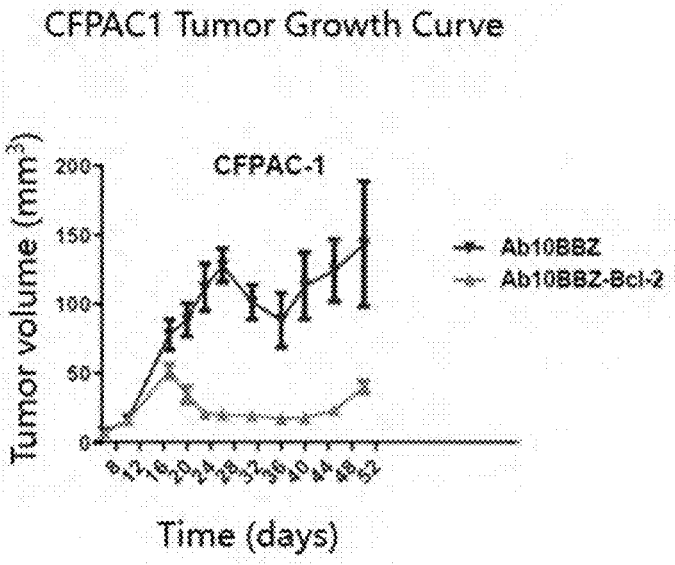

CFPAC1 Tumor Growth Curve
CFPAC-1
Tumor volume (mm3)
200
150
100
50
0
Ab10BBZ
Ab10BBZ-Bcl-2
Time (days)

Fig. 9

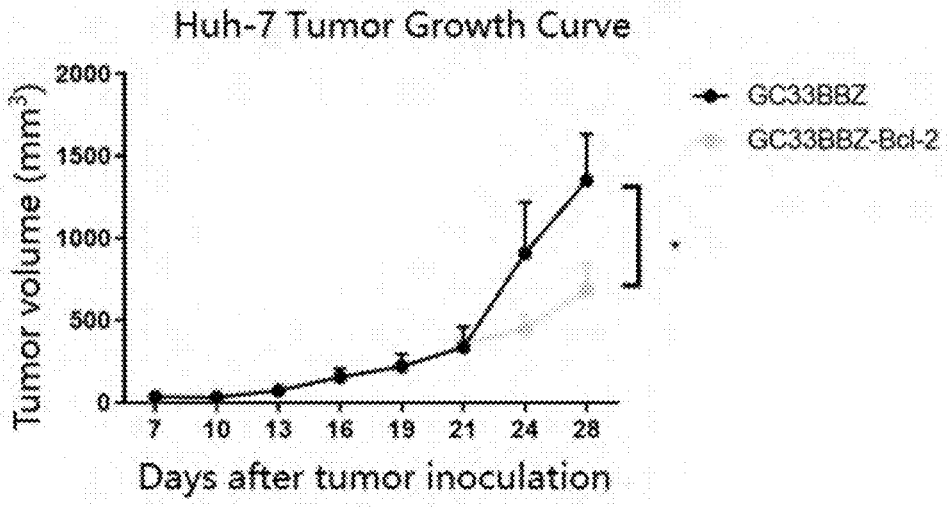

Huh-7 Tumor Growth Curve
Tumor volume (mm3)
2000
1500
1000
500
0
7
10
13
16
19
21
24
28
Days after tumor inoculation
GC33BBZ
GC33BBZ-Bcl-2
*

Fig. 10

MODIFIED IMMUNE EFFECTOR CELL AND USE THEREOF

FIELD OF THE INVENTION

[0001] The present application relates to the field of biomedicine, and specifically to a modified CAR-T cell and a use thereof.

BACKGROUND OF THE INVENTION

[0002] CLDN18 is a member of the Claudins protein family, and CLDN18.1 and CLDN18.2 are alternative splicing forms of CLDN18. In normal tissues, CLDN18.1 is mainly expressed in lung, and CLDN18.2 is only expressed on gastric mucosal epithelium cells. However, CLDN18.2 is expressed in a variety of tumor tissues, such as gastric cancer, pancreatic cancer, esophagus cancer, ovarian cancer, lung cancer, etc., and is an ideal target for tumor CAR-T therapy.

[0003] CD20 is specifically expressed in B cells or leukemia or lymphoma derived from B cells. MabThera, an antibody drug targeting CD20, has been marketed, but there are drug resistance and recurrence during the treatment.

[0004] Glypican-3 (GPC-3) is not expressed in normal liver tissues but is highly expressed in fetal liver and liver cancer tissues. It is a specific marker for primary hepatocellular carcinoma and is involved in the development and progression of liver cancer, therefore, it is a target for the small molecule targeted therapy of liver cancer, as well as a recognition target for immunotherapy.

[0005] In adoptive cell therapy, chimeric antigen receptor T cells (CAR-T cells) are artificially modified tumor killing cells, which combine the target recognition function of antibodies and the tumor killing function of T cells and thus become a major breakthrough in the field of tumor immunotherapy. However, the efficacy of CAR-T on the treatment of solid tumors such as gastric cancer and pancreatic cancer is not satisfactory, and novel CAR-T therapies are the key to the treatment of solid tumors.

SUMMARY OF THE INVENTION

[0006] The present application provides an immune effector cell, which includes and/or expresses a chimeric antigen receptor (CAR), and a Bcl-2 protein or a functionally active fragment thereof. The immune effector cell has one or more of the following properties: 1) capable of specifically binding to an antigen; 2) having a strong in vitro expansion ability; 3) having a strong in vivo anti-tumor ability; 4) having a strong in vitro anti-tumor ability.

[0007] In one aspect, the present application provides an immune effector cell, which includes and/or expresses a chimeric antigen receptor (CAR) and a Bcl-2 protein or a functionally active fragment thereof.

[0008] In some embodiments, the CAR includes an antigen binding domain, and the antigen binding domain includes an antibody specifically binding to CD20 or an antigen binding fragment thereof.

[0009] In some embodiments, the antibody or the antigen binding fragment thereof includes a HCDR3, and the HCDR3 includes an amino acid sequence as set forth in SEQ ID NO: 1.

[0010] In some embodiments, the antibody or the antigen binding fragment thereof includes a HCDR2, and the HCDR2 includes an amino acid sequence as set forth in SEQ ID NO: 2.

[0011] In some embodiments, the antibody or the antigen binding fragment thereof includes a HCDR1, and the HCDR1 includes an amino acid sequence as set forth in SEQ ID NO: 3.

[0012] In some embodiments, the antibody or the antigen binding fragment thereof includes a LCDR3, and the LCDR3 includes an amino acid sequence as set forth in SEQ ID NO: 4.

[0013] In some embodiments, the antibody or the antigen binding fragment thereof includes a LCDR2, and the LCDR2 includes an amino acid sequence as set forth in SEQ ID NO: 5.

[0014] In some embodiments, the antibody or the antigen binding fragment thereof includes a LCDR1, and the LCDR1 includes an amino acid sequence as set forth in SEQ ID NO: 6.

[0015] In some embodiments, the antibody or the antigen binding fragment thereof includes a VH, and the VH includes an amino acid sequence as set forth in SEQ ID NO: 7.

[0016] In some embodiments, the antibody or the antigen binding fragment thereof includes a VL, and the VL includes an amino acid sequence as set forth in SEQ ID NO: 8.

[0017] In some embodiments, the antibody or the antigen binding fragment thereof includes an amino acid sequence as set forth in SEQ ID NO: 10.

[0018] In some embodiments, the CAR includes an antigen binding domain, and the antigen binding domain includes an antibody specifically binding to CLDN18.2 or an antigen binding fragment thereof.

[0019] In some embodiments, the antibody or the antigen binding fragment thereof includes a HCDR3, and the HCDR3 includes an amino acid sequence as set forth in SEQ ID NO: 11.

[0020] In some embodiments, the antibody or the antigen binding fragment thereof includes a HCDR2, and the HCDR2 includes an amino acid sequence as set forth in SEQ ID NO: 12.

[0021] In some embodiments, the antibody or the antigen binding fragment thereof includes a HCDR1, and the HCDR1 includes an amino acid sequence as set forth in SEQ ID NO: 13.

[0022] In some embodiments, the antibody or the antigen binding fragment thereof includes a LCDR3, and the LCDR3 includes an amino acid sequence as set forth in SEQ ID NO: 14.

[0023] In some embodiments, the antibody or the antigen binding fragment thereof includes a LCDR2, and the LCDR2 includes an amino acid sequence as set forth in SEQ ID NO: 15.

[0024] In some embodiments, the antibody or the antigen binding fragment thereof includes a LCDR1, and the LCDR1 includes an amino acid sequence as set forth in SEQ ID NO: 16.

[0025] In some embodiments, the antibody or the antigen binding fragment thereof includes a VH, and the VH includes an amino acid sequence as set forth in SEQ ID NO: 17.

[0026] In some embodiments, the antibody or the antigen binding fragment thereof includes a VL, and the VL includes an amino acid sequence as set forth in SEQ ID NO: 18.

[0027] In some embodiments, the antibody or the antigen binding fragment thereof includes an amino acid sequence as set forth in SEQ ID NO: 19.

[0028] In some embodiments, the CAR includes an antigen binding domain, and the antigen binding domain includes an antibody specifically binding to GPC-3 or an antigen binding fragment thereof.

[0029] In some embodiments, the antibody or the antigen binding fragment thereof includes a HCDR3, and the HCDR3 includes an amino acid sequence as set forth in any one of SEQ ID NO: 20, SEQ ID NO: 29, and SEQ ID NO: 38.

[0030] In some embodiments, the antibody or the antigen binding fragment thereof includes a HCDR2, and the HCDR2 includes an amino acid sequence as set forth in any one of SEQ ID NO: 21, SEQ ID NO: 30, and SEQ ID NO: 39.

[0031] In some embodiments, the antibody or the antigen binding fragment thereof includes a HCDR1, and the HCDR1 includes an amino acid sequence as set forth in any one of SEQ ID NO: 22, SEQ ID NO: 31, and SEQ ID NO: 40.

[0032] In some embodiments, the antibody or the antigen binding fragment thereof includes a LCDR3, and the LCDR3 includes an amino acid sequence as set forth in any one of SEQ ID NO: 23, SEQ ID NO: 32, and SEQ ID NO: 41.

[0033] In some embodiments, the antibody or the antigen binding fragment thereof includes a LCDR2, and the LCDR2 includes an amino acid sequence as set forth in any one of SEQ ID NO: 24, SEQ ID NO: 33, and SEQ ID NO: 42.

[0034] In some embodiments, the antibody or the antigen binding fragment thereof includes a LCDR1, and the LCDR1 includes an amino acid sequence as set forth in any one of SEQ ID NO: 25, SEQ ID NO: 34, and SEQ ID NO: 43.

[0035] In some embodiments, the antibody or the antigen binding fragment thereof includes a VH, and the VH includes an amino acid sequence as set forth in any one of SEQ ID NO: 26, SEQ ID NO: 35, and SEQ ID NO: 44.

[0036] In some embodiments, the antibody or the antigen binding fragment thereof includes a VL, and the VL includes an amino acid sequence as set forth in any one of SEQ ID NO: 27, SEQ ID NO: 36, and SEQ ID NO: 45.

[0037] In some embodiments, the antibody or the antigen binding fragment thereof includes an amino acid sequence as set forth in any one of SEQ ID NO: 28, SEQ ID NO: 37, and SEQ ID NO: 46.

[0038] In some embodiments, the antibody includes a single-chain antibody.

[0039] In some embodiments, the CAR includes a transmembrane domain, and the transmembrane domain includes a transmembrane domain derived from a protein selected from the group consisting of: CD28, CD3e, CD45, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137, and CD154.

[0040] In some embodiments, the transmembrane domain includes an amino acid sequence as set forth in SEQ ID NO: 47.

[0041] In some embodiments, the CAR includes a co-stimulatory domain, and the co-stimulatory domain includes one or more co-stimulatory domains of a protein selected from the group consisting of: co-stimulatory signaling regions in CD28, 4-1BB, CD40L, TIM1, CD226, DR3, SLAM, ICOS, OX40, NKG2D, 2B4, CD244, FcεRIγ, BTLA, CD27, CD30, GITR, HVEM, DAP10, CD2, NKG2C, LIGHT, and DAP12.

[0042] In some embodiments, the co-stimulatory domain includes an amino acid sequence as set forth in SEQ ID NO: 48.

[0043] In some embodiments, the CAR includes an intracellular signaling domain, and the intracellular signaling domain includes an intracellular signaling domain derived from CD3.

[0044] In some embodiments, the intracellular signaling domain includes an amino acid sequence as set forth in SEQ ID NO: 49.

[0045] In some embodiments, the CAR includes a hinge region, and the hinge region is located between the antigen binding domain and the transmembrane domain.

[0046] In some embodiments, the hinge region includes at least one of hinge regions of CD8, CD28, 4-1BB, CD4, CD27, CD7, and PD-1.

[0047] In some embodiments, the hinge region includes an amino acid sequence as set forth in SEQ ID NO: 50.

[0048] In some embodiments, the CAR includes an amino acid sequence as set forth in any one of SEQ ID NO: 53, SEQ ID NO: 55, SEQ ID NO: 57, SEQ ID NO: 59, and SEQ ID NO: 61.

[0049] In some embodiments, the Bcl-2 protein or the functionally active fragment thereof includes an exogenous Bcl-2 protein or a functionally active fragment thereof.

[0050] In some embodiments, the Bcl-2 protein or the functionally active fragment thereof includes an amino acid sequence as set forth in SEQ ID NO: 52.

[0051] In some embodiments, the immune effector cell includes T cells.

[0052] In another aspect, the present application further provides a nucleic acid molecule encoding the CAR and the Bcl-2 protein or the functionally active fragment thereof.

[0053] In some embodiments, the nucleic acid molecule includes a sequence encoding a self-cleaving peptide located between a sequence encoding the CAR and a sequence encoding the Bcl-2 protein.

[0054] In some embodiments, the self-cleaving peptide includes a 2A peptide.

[0055] In some embodiments, the 2A peptide is one or more selected from the group consisting of: P2A, T2A, E2A, and F2A.

[0056] In some embodiments, the 2A peptide includes an amino acid sequence as set forth in SEQ ID NO: 51.

[0057] In another aspect, the present application further provides a vector including the nucleic acid molecule.

[0058] In some embodiments, the vector is selected from one or more of plasmids, retroviral vectors, and lentiviral vectors.

[0059] In another aspect, the present application further provides an immune effector cell including the nucleic acid molecule or the vector.

[0060] In another aspect, the present application further provides a method for preparing the immune effector cell,

which includes culturing the immune effector cell under conditions allowing the expression of the chimeric antigen receptor.

[0061] In another aspect, the present application further provides a composition including the immune effector cell.

[0062] In another aspect, the present application further provides use of the immune effector cell, the nucleic acid molecule, the vector, or the composition in the preparation of drugs for preventing and/or treating diseases and/or disorders.

[0063] In another aspect, the present application further provides the immune effector cell, the nucleic acid molecule, the vector, or the composition, which is used for preventing and/or treating diseases and/or disorders.

[0064] In another aspect, the present application further provides a method for preventing and/or treating diseases and/or disorders, and the method includes administering to a subject in need the immune effector cell, the nucleic acid molecule, the vector, or the composition of the present application.

[0065] In some embodiments, the diseases and/or disorders are associated with the expression of CD20.

[0066] In some embodiments, the diseases and/or disorders are associated with the expression of CLDN18.2.

[0067] In some embodiments, the diseases and/or disorders are associated with the expression of GPC-3.

[0068] In some embodiments, the diseases and/or disorders include tumors.

[0069] In some embodiments, the tumors include solid tumors and/or blood tumors.

[0070] In some embodiments, the tumors include CD20 positive tumors.

[0071] In some embodiments, the tumors include CLDN18.2 positive tumors.

[0072] In some embodiments, the tumors include GPC-3 positive tumors.

[0073] In some embodiments, the tumors include lymphoma.

[0074] In some embodiments, the tumors include pancreatic cancer.

[0075] Those skilled in the art can easily perceive other aspects and advantages of the present application from the detailed description below. In the following detailed description, only exemplary embodiments of the present application are shown and described. As those skilled in the art will recognize, the content of the present application enables those skilled in the art to make changes to the disclosed specific embodiments without departing from the spirit and scope of the invention involved in the present application. Correspondingly, the drawings and descriptions in the specification of the present application are merely exemplary, rather than restrictive.

BRIEF DESCRIPTION OF THE DRAWINGS

[0076] The specific features of the invention involved in the present application are shown in the appended claims. The characteristics and advantages of the invention involved in the present application can be better understood by referring to the exemplary embodiments and the accompanying drawings described in detail below. A brief description of the drawings is as follows:

[0077] FIG. **1** shows a schematic diagram of the construction of the chimeric antigen receptor of the present application.

[0078] FIGS. **2**A-**2**B show the expression profile of the CAR of the present application.

[0079] FIG. **3** shows the expression profile of the CAR of the immune effector cell of the present application.

[0080] FIG. **4** shows the expansion capacity of anti-CD20 Bcl-2 CAR-T cells.

[0081] FIG. **5** shows the expansion capacity of anti-CLDN18.2 Bcl-2 CAR-T cells.

[0082] FIG. **6** shows the expansion capacity of anti-GPC-3 Bcl-2 CAR-T cells.

[0083] FIG. **7** shows the in vitro tumor killing capacity of the immune effector cell of the present application.

[0084] FIGS. **8**A-**8**B show the in vivo tumor killing capacity of the immune effector cell of the present application.

[0085] FIG. **9** shows the effect of anti-CLDN18.2 Bcl-2 CAR-T cells on tumor size.

[0086] FIG. **10** shows the in vivo tumor killing capacity of anti-GPC-3 Bcl-2 CAR-T cells.

DETAILED DESCRIPTION OF THE EMBODIMENTS

[0087] The implementation of the present application will be illustrated in the following specific examples, and other advantages and effects of the present application will be easily known by those familiar with this technology from the content disclosed in the specification.

DEFINITION OF TERMS

[0088] In the present application, the term "immune effector cell" generally refers to an immune cell that is involved in the immune response and performs an effector function. For example, the exercise of an effector function may include removal of foreign antigens or promotion of immune effector responses. The immune effector cells may include plasmocytes, T cells, B cells, natural killer (NK) cells, natural killer T (NKT) cells, mastocytes, and bone marrow-derived phagocytes. The immune effector cell of the present application may include engineered immune effector cells. For example, the immune effector cell of the present application may include a chimeric antigen receptor and may also express a Bcl-2 protein or a functionally active fragment thereof. For example, the Bcl-2 protein is an exogenous Bcl-2 protein or a functionally active fragment thereof.

[0089] In the present application, the term "chimeric antigen receptor" or "CAR", also referred to as "chimeric receptor", "T receptor", or chimeric immune receptor, generally refers to a recombinant polypeptide construct including at least a extracellular antigen binding domain, a transmembrane domain and a cytoplasmic signaling domain (also referred to as "intracellular signaling domain"). For example, the chimeric antigen receptor may include a targeting moiety (e.g., the moiety binding to a tumor-related antigen), a hinge region, a transmembrane domain, a co-stimulatory domain, and an intracellular signaling domain.

[0090] The terms "Bcl-2" and "Bcl-2 protein" may be used interchangeably and generally refer to the encoded products of bcl-2 proto-oncogenes. In some embodiments, the amino acid sequence of Bcl-2 protein may be as set forth in SEQ ID NO: 52. In the present application, the term covers full-length Bcl-2 proteins and homologues, analogues, truncations, mutants, and functionally active frag-

ments thereof. In the present application, the term covers exogenous Bcl-2 proteins or functionally active fragments thereof.

[0091] In the present application, the term "antigen binding domain" generally refers to a domain capable of binding to a target antigen. The antigen binding domain may include a chimeric antigen receptor, a fragment thereof, an antibody or an antigen binding fragment thereof, which is capable of (specifically) binding to an antigen. The antigen binding domain may be of natural, synthetic, semi-synthetic or recombinant origin. In some embodiments, the antigen binding domain may include an antibody or an antigen binding fragment thereof. For example, the antigen binding domain may include a single-chain antibody.

[0092] In the present application, the term "specifically binding to" or "specific" generally refers to measurable and reproducible interactions, e.g., the binding between a target and an antibody, and may determine the presence of a target in the presence of a heterogeneous population of molecules (including biomolecules). For example, the antibody that specifically binds a target (that may be an epitope) may be an antibody that binds the target with greater affinity, avidity, easier, and/or for a longer duration than it binds other targets. In some embodiments, the antibody specifically binds an epitope on a protein, the epitope being conserved in different species of proteins. In some embodiments, specific binding may include but does not require exclusive binding.

[0093] In the present application, the term "antibody" generally refers to a polypeptide molecule capable of specifically recognizing and/or neutralizing a particular antigen. For example, the antibody may include an immunoglobulin composed of at least two heavy (H) chains and two light (L) chains linked to each other through disulfide bonds, and includes any molecules containing the antigen binding moiety. The term "antibody" includes monoclonal antibodies, antibody fragments or antibody derivatives, including, but not limited to, human antibodies, humanized antibodies, chimeric antibodies, single-domain antibodies (e.g., dAb), single-chain antibodies (e.g., scFv), and antibody fragments binding to antigens (e.g., Fab, Fab' and $(Fab)_2$ fragments). The term "antibody" also includes all recombinant forms of the antibody, for example, antibodies expressed in prokaryotic cells, unglycosylated antibodies, as well as any antibody fragments binding to antigens of the present application and derivatives thereof. Each heavy chain may be composed of a heavy chain variable region (VH) and a heavy chain constant region. Each light chain may be composed of a light chain variable region (VL) and a light chain constant region. VH and VL regions may be further distinguished into highly variable regions called complementary determining regions (CDRs), which are interspersed in more conserved regions called framework regions (FRs). Each of VH and VL may be composed of three CDRs and four FRs, which can be arranged in the following order from the amino terminus to the carboxyl terminus: FR1, CDR1, FR2, CDR2, FR3, CDR3, and FR4. The heavy chain and light chain variable regions contain binding domains interacting with antigens.

[0094] In the present application, the term "CDR", also referred to as "complementary determining region", generally refers to a region in the variable domain of an antibody, the sequence of which is highly variable and/or forms the structure-defining loop. Generally, an antibody includes six CDRs; three in VH (HCDR1, HCDR2, HCDR3), and three in VL (LCDR1, LCDR2, LCDR3). In some embodiments, naturally occurring camelid antibodies composed only of heavy chains may also function normally and stably in the absence of light chains. See, e.g., Hamers-Casterman et al., Nature 363: 446-448 (1993); Sheriff et al, Nature Struct. Biol. 3:733-736 (1996). The CDRs of an antibody may be determined by various coding systems, such as CCG, Kabat, Chothia, IMGT, comprehensive consideration of Kabat/Chothia, etc. These coding systems are known in the art, specifically see, e.g., http://www.bioinf.org.uk/abs/index.html #kabatnum. For example, the amino acid sequence number of the antibody may follow the IMGT numbering scheme (IMGT, the international ImMunoGeneTics information system@imgt.cines.fr; http://imgt.cines.fr; Lefranc et, al., 1999, Nucleic Acids Res. 27: 209-212; Ruiz et, al., 2000 Nucleic Acids Res. 28: 219-221; Lefranc et, al., 2001, Nucleic Acids Res. 29:207-209; Lefranc et, al., 2003, Nucleic Acids Res. 31: 307-310; Lefranc et, al., 2005, DevComp Immunol 29: 185-203). For example, the CDRs of the antibody may be determined by the Kabat numbering system (see e.g., Kabat E A &Wu T T (1971) Ann NY AcadSci 190:382-391 and Kabat E A et al., (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242).

[0095] In the present application, the term "FR" generally refers to the more highly conserved portions of the variable domain of an antibody, which are referred to as framework regions. Generally, the variable domains of natural heavy chains and light chains each include four FRs, i.e., four in VH (H-FR1, H-FR2, H-FR3, and H-FR4), and four in VL (L-FR1, L-FR2, L-FR3, and L-FR4).

[0096] In the present application, the terms "variable domain" and "variable region" may be used interchangeably and generally refer to a portion of the heavy chain and/or light chain of an antibody. The variable domains of heavy chains and light chains may be respectively referred to as "VII" and "V_L" (or referred to as "VH" and "VL", respectively). These domains are usually the most variable part of an antibody (relative to other antibodies of the same type) and include antigen binding sites.

[0097] In the present application, the term "single-chain antibody (scFv)" generally refers to a fusion protein including at least one antibody fragment containing a light chain variable region and at least one antibody fragment containing a heavy chain variable region. Where, the light chain variable region and the heavy chain variable region are contiguous (e.g., via a synthetic linker, such as a short flexible polypeptide linker). The scFv may be expressed as a single-chain polypeptide, and may also retain the specificity of the intact antibody from which it is derived. In the present application, the scFv may contain the VL and VH in any order (e.g., relative to the N terminus and C terminus of the polypeptide), and the scFv may also include VL-linker-VH or VH-linker-VL.

[0098] In the present application, the term "transmembrane domain" generally refers to a domain capable of spanning the cytoplasmic membrane. The transmembrane domain may usually contain three structural regions: an N-terminal extracellular region, an intermediate transmembrane extension region, and a C-terminal cytoplasmic region. The transmembrane domain may also contain an intracellular region or a cytoplasmic region.

[0099] In the present application, the term "co-stimulatory domain" generally refers to an intracellular domain that can

provide immune co-stimulatory molecules. Where, the co-stimulatory molecules may be cell surface molecule required for an effective response of the lymphocyte to the antigen. In some embodiments, the co-stimulatory domain may be the intracellular part of the co-stimulatory molecules or the truncated forms thereof.

[0100] In the present application, the term "intracellular signaling domain" generally refers to a domain located inside a cell capable of conducting signals. In the present application, the intracellular signaling domain can conduct signals into the cells. The term covers intracellular signaling domains capable of inducing effector function signals and any truncated portions thereof.

[0101] In the present application, the term "4-1BB", also referred to as "CD137", generally refers to a member of the tumor necrosis factor (TNF) receptor family and is encoded by the tumor necrosis factor receptor superfamily member 9 (TNFRSF9) gene. The amino acid sequence of human 4-1BB can be found in GenBank Accession Number No. AAA62478.2. The 4-1BB of the present application covers the homologues, analogues, or mutants thereof.

[0102] In the present application, the "vector" generally refers to a nucleic acid molecule capable of self-replication in a suitable host, which is used to transfer the inserted nucleic acid molecule into and/or between host cells. The vector may include a vector mainly used for inserting DNA or RNA into cells, a vector mainly used for replicating DNA or RNA, and a vector mainly used for expression of DNA or RNA transcription and/or translation. The vector also includes a vector with a variety of the above functions. The vector may be a polynucleotide that can be transcribed and translated into a polypeptide when introduced into a suitable host cell. Generally, by culturing a suitable host cell containing the vector, the vector can produce the desired expression products.

[0103] In the present application, the term "plasmid" generally refers to DNA molecules other than chromosomes or nucleoids in organisms such as bacteria and yeast, which is present in the cytoplasm and have the ability to replicate autonomously, enabling them to maintain a constant copy number in offspring cells and express the genetic information carried. In genetic engineering research, plasmids are used as gene vectors.

[0104] In the present application, the term "retroviral vector" generally refers to viral particles that can control and express exogenous genes but cannot self-package into proliferative virus particles. Such viruses mostly contain reverse transcriptase. Retroviruses contain at least three genes: gag which contains the gene for the protein that makes up the center and structure of the virus; pol which contains the gene for the reverse transcriptase; and env which contains the gene that makes up the outer shell of the virus. Through retroviral transfection, retroviral vectors can randomly and stably integrate their own genome and the exogenous genes they carry into the host cell genome, for example, they can integrate CAR molecules into the host cell.

[0105] In the present application, the term "lentiviral vector" generally refers to a diploid RNA viral vector that is a retrovirus. Lentiviral vectors are vectors prepared by, based on the genome of the lentivirus, removing multiple sequence structures related to the viral activity to make it biologically safe, and then introducing the sequence and expression structure of the target gene required for the experiment into the genome backbone. Through lentiviral vector transfection, retroviral vectors can randomly and stably integrate their own genome and the exogenous genes they carry into the host cell genome, for example, they can integrate CAR molecules into the host cell.

[0106] The term "tumor" generally refers to any new pathological tissue hyperplasia. Tumor cells may spread to other parts of the body locally or through the bloodstream and lymphatic system. In the present application, the tumors may include benign tumors and malignant tumors. In the present application, the tumors may include solid tumors and/or blood tumors. In the present application, the tumors may include cancers. In the present application, examples of tumors include, but not limited to brain glioma, breast cancer, melanoma, non-small cell lung cancer, bladder cancer, ovarian cancer, and colorectal cancer.

[0107] In the present application, it should also be understood that the involved protein, polypeptide and/or amino acid sequences includes at least the following scope: variants or homologues having the same or similar functions as the protein or polypeptide.

[0108] In the present application, the variants may be proteins or polypeptides with one or more amino acid substitutions, deletions, or additions in the amino acid sequence of the protein and/or the polypeptide (e.g., antibodies or fragments thereof that specifically bind to CD73 protein). For example, the functional variants may include proteins or polypeptides with amino acid changes by at least 1, for example, 1-30, 1-20 or 1-10, and further for example 1, 2, 3, 4 or 5 amino acid substitutions, deletions and/or insertions. The functional variants may substantially retain the biological properties of the protein or the polypeptide before change (e.g., substitution, deletion, or addition). For example, the functional variants may retain at least 60%, 70%, 80%, 90%, or 100% of the biological activity (e.g., antigen-binding ability) of the protein or the polypeptide before change. For example, the substitution may be conservative substitution.

[0109] In the present application, the homologues may be proteins or polypeptides having at least about 85% (e.g., having at least about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99% or higher) sequence homology with the amino acid sequence of the protein and/or the polypeptide (e.g., antibodies or fragments thereof that specifically bind to CD73 protein).

[0110] In the present application, the homology generally refers to similarity, analogy or association between two or more sequences. The "percentage of sequence homology" can be calculated as below: comparing two sequences to be compared in a comparison window, determining the number of positions where the same nucleic acid bases (e.g., A, T, C, G, I) or the same amino acid residues (e.g., Ala, Pro, Ser, Thr, Gly, Val, Leu, Ile, Phe, Tyr, Trp, Lys, Arg, His, Asp, Glu, Asn, Gln, Cys, and Met) are present in both sequences so as to obtain the number of matching positions, dividing the number of matching positions by the total number of positions in the comparison window (i.e., window size), multifying the result by 100 to generate the percentage of sequence homology. The alignment for determining the percentage of sequence homology can be achieved in a variety of ways known in the art, for example, by using publicly available computer software, such as BLAST, BLAST-2. ALIGN, or Megalign (DNASTAR) software. A

person skilled in the art can determine suitable parameters for aligning sequences, including any algorithms needed to achieve the maximal alignment over the full-length sequence range being compared or within the target sequence region. The homology can also be determined by the following methods: FASTA and BLAST. The description of FASTA algorithm can be found in "Improved tools for biological sequence comparison" to W. R. Pearson and D. J. Lipman. Proc. Nat. Acad. Sci., 85: 2444-2448, 1988; and "Rapid and Sensitive Protein Similarity Searches" to D. J. Lipman and W. R. Pearson, Science, 227: 1435-1441, 1989. The description of BLAST algorithm can be found in "Basic Local Alignment Search Tool" to S. Altschul, W. Gish, W Miller. E. W, Myers, and D. Lipman. Journal of Molecular Biology, 215:403-410, 1990.

[0111] In the present application, the term "include" generally refers to the meaning of comprising, encompassing, containing, or embracing. In some cases, it also means "is/are" or "be composed of".

[0112] In the present application, the term "about" generally refers to varying in a range of 0.5%-10% above or below a specified value, for example, varying in a range of 0.5%, 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, 5%, 5.5%, 6%, 65%, 7%, 7.5%, 8%, 8.5%, 9%, 9.5%, or 10% above or below a specified value.

DETAILED DESCRIPTION OF THE INVENTION

[0113] Immune Effector Cell

[0114] In one aspect, the present application provides an immune effector cell, which may include and/or express a chimeric antigen receptor (CAR), and the immune effector cell may further include and/or express a Bcl-2 protein or a functionally active fragment thereof. The Bcl-2 protein or the functionally active fragment thereof may be introduced into the immune effector cell exogenously (e.g., artificially synthesizing the following sequences: a hinge region, a transmembrane domain, a co-stimulatory domain, an intracellular signaling domain, a cleavage peptide, and a Bcl-2 or a functionally active fragment thereof, linking the various parts and then adding scFv, molecule cloning to produce viral vectors, and infecting the immune effector cell for expression). For example, the immune effector cell (e.g., T cells) may be an engineered or modified immune effector cell (e.g., T cells), wherein the engineering may include introducing into the immune effector cell (e.g., immune effector cells from other natural sources derived from subjects) the CAR and/or the Bcl-2 protein, and/or nucleic acid molecules expressing the CAR and/or the Bcl-2 protein (e.g., by constructing nucleic acid sequences encoding the antigen binding protein, hinge region, transmembrane domain, co-stimulatory domain, intracellular signaling domain, cleavage peptide, and Bcl-2, and infecting the immune effector cell with the viral vector for expression). In some embodiments, the CAR includes an antigen binding domain, a transmembrane domain, a co-stimulatory domain, an intracellular signaling domain, and/or a hinge region. In some embodiments, the immune effector cell over-expresses the Bcl-2 protein or the functionally active fragment thereof.

[0115] In some embodiments, the CAR includes an antigen binding domain, and the antigen binding domain includes an antibody targeting CD20 or an antigen binding fragment thereof.

[0116] In some embodiments, the antibody targeting CD20 or the antigen binding fragment thereof includes a HCDR3, and the HCDR3 includes an amino acid sequence as set forth in SEQ ID NO: 1; in some embodiments, the antibody or the antigen binding fragment thereof includes a HCDR2, and the HCDR2 includes an amino acid sequence as set forth in SEQ ID NO: 2; in some embodiments, the antibody or the antigen binding fragment thereof includes a HCDR1, and the HCDR1 includes an amino acid sequence as set forth in SEQ ID NO: 3. In some embodiments, the antibody or the antigen binding fragment thereof includes a LCDR3, and the LCDR3 includes an amino acid sequence as set forth in SEQ ID NO: 4; in some embodiments, the antibody or the antigen binding fragment thereof includes a LCDR2, and the LCDR2 includes an amino acid sequence as set forth in SEQ ID NO: 5; in some embodiments, the antibody or the antigen binding fragment thereof includes a LCDR1, and the LCDR1 includes an amino acid sequence as set forth in SEQ ID NO: 6.

[0117] In some embodiments, the antibody or the antigen binding fragment thereof includes a HCDR3, a HCDR2, and a HCDR1, the HCDR3 includes an amino acid sequence as set forth in SEQ ID NO: 1, the HCDR2 includes an amino acid sequence as set forth in SEQ ID NO: 2, and the HCDR1 includes an amino acid sequence as set forth in SEQ ID NO: 3.

[0118] In some embodiments, the antibody or the antigen binding fragment thereof includes a LCDR3, a LCDR2, and a LCDR1, the LCDR3 includes an amino acid sequence as set forth in SEQ ID NO: 4, the LCDR2 includes an amino acid sequence as set forth in SEQ ID NO: 5, and the LCDR1 includes an amino acid sequence as set forth in SEQ ID NO: 6.

[0119] In some embodiments, the antibody or the antigen binding fragment thereof includes a HCDR3, a HCDR2, a HCDR1, a LCDR3, a LCDR2, and a LCDR1, the HCDR3 includes an amino acid sequence as set forth in SEQ ID NO: 1, the HCDR2 includes an amino acid sequence as set forth in SEQ ID NO: 2, the HCDR1 includes an amino acid sequence as set forth in SEQ ID NO: 3, the LCDR3 includes an amino acid sequence as set forth in SEQ ID NO: 4, the LCDR2 includes an amino acid sequence as set forth in SEQ ID NO: 5, and the LCDR1 includes an amino acid sequence as set forth in SEQ ID NO: 6.

[0120] In some embodiments, the antibody or the antigen binding fragment thereof includes a VH, and the VH may include an amino acid sequence as set forth in SEQ ID NO: 7. In some embodiments, the antibody or the antigen binding fragment thereof includes a VL, and the VL may include an amino acid sequence as set forth in SEQ ID NO: 8.

[0121] In some embodiments, the antibody or the antigen binding fragment thereof includes a VH and a VL, the VH includes an amino acid sequence as set forth in SEQ ID NO: 7 and the VL includes an amino acid sequence as set forth in SEQ ID NO: 8.

[0122] In some embodiments, the antibody or the antigen binding fragment thereof includes an amino acid sequence as set forth in SEQ ID NO: 10.

[0123] In some embodiments, the CAR includes an antigen binding domain, and the antigen binding domain includes an antibody targeting CLDN18.2 or an antigen binding fragment thereof.

[0124] In some embodiments, the antibody targeting CLDN18.2 or the antigen binding fragment thereof includes

a HCDR3, and the HCDR3 includes an amino acid sequence as set forth in SEQ ID NO: 11; in some embodiments, the antibody or the antigen binding fragment thereof includes a HCDR2, and the HCDR2 includes an amino acid sequence as set forth in SEQ ID NO: 12; in some embodiments, the antibody or the antigen binding fragment thereof includes a HCDR1, and the HCDR1 includes an amino acid sequence as set forth in SEQ ID NO: 13. In some embodiments, the antibody or the antigen binding fragment thereof includes a LCDR3, and the LCDR3 includes an amino acid sequence as set forth in SEQ ID NO: 14; in some embodiments, the antibody or the antigen binding fragment thereof includes a LCDR2, and the LCDR2 includes an amino acid sequence as set forth in SEQ ID NO: 15; in some embodiments, the antibody or the antigen binding fragment thereof includes a LCDR1, and the LCDR1 includes an amino acid sequence as set forth in SEQ ID NO: 16.

[0125] In some embodiments, the antibody or the antigen binding fragment thereof includes a HCDR3, a HCDR2, and a HCDR1, the HCDR3 includes an amino acid sequence as set forth in SEQ ID NO: 11, the HCDR2 includes an amino acid sequence as set forth in SEQ ID NO: 12, and the HCDR1 includes an amino acid sequence as set forth in SEQ ID NO: 13.

[0126] In some embodiments, the antibody or the antigen binding fragment thereof includes a LCDR3, a LCDR2, and a LCDR1, the LCDR3 includes an amino acid sequence as set forth in SEQ ID NO: 14, the LCDR2 includes an amino acid sequence as set forth in SEQ ID NO: 15, and the LCDR1 includes an amino acid sequence as set forth in SEQ ID NO: 16.

[0127] In some embodiments, the antibody or the antigen binding fragment thereof includes a HCDR3, a HCDR2, a HCDR1, a LCDR3, a LCDR2, and a LCDR1, the HCDR3 includes an amino acid sequence as set forth in SEQ ID NO: 11, the HCDR2 includes an amino acid sequence as set forth in SEQ ID NO: 12, the HCDR1 includes an amino acid sequence as set forth in SEQ ID NO: 13, the LCDR3 includes an amino acid sequence as set forth in SEQ ID NO: 14, the LCDR2 includes an amino acid sequence as set forth in SEQ ID NO: 15, and the LCDR1 includes an amino acid sequence as set forth in SEQ ID NO: 16.

[0128] In some embodiments, the antibody or the antigen binding fragment thereof includes a VH, and the VH may include an amino acid sequence as set forth in SEQ ID NO: 17. In some embodiments, the antibody or the antigen binding fragment thereof includes a VL, and the VL includes an amino acid sequence as set forth in SEQ ID NO: 18.

[0129] In some embodiments, the antibody or the antigen binding fragment thereof includes a VH and a VL, the VH includes an amino acid sequence as set forth in SEQ ID NO: 17 and the VL includes an amino acid sequence as set forth in SEQ ID NO: 18.

[0130] In some embodiments, the antibody or the antigen binding fragment thereof includes an amino acid sequence as set forth in SEQ ID NO: 19.

[0131] In some embodiments, the CAR includes an antigen binding domain, and the antigen binding domain includes an antibody targeting GPC-3 or an antigen binding fragment thereof.

[0132] In some embodiments, the antibody targeting GPC-3 or the antigen binding fragment thereof includes a HCDR3, and the HCDR3 includes an amino acid sequence as set forth in SEQ ID NO: 20; in some embodiments, the antibody or the antigen binding fragment thereof includes a HCDR2, and the HCDR2 includes an amino acid sequence as set forth in SEQ ID NO: 21; in some embodiments, the antibody or the antigen binding fragment thereof includes a HCDR1, and the HCDR1 includes an amino acid sequence as set forth in SEQ ID NO: 22. In some embodiments, the antibody or the antigen binding fragment thereof includes a LCDR3, and the LCDR3 includes an amino acid sequence as set forth in SEQ ID NO: 23; in some embodiments, the antibody or the antigen binding fragment thereof includes a LCDR2, and the LCDR2 includes an amino acid sequence as set forth in SEQ ID NO: 24; in some embodiments, the antibody or the antigen binding fragment thereof includes a LCDR1, and the LCDR1 includes an amino acid sequence as set forth in SEQ ID NO: 25.

[0133] In some embodiments, the antibody or the antigen binding fragment thereof includes a HCDR3, a HCDR2, and a HCDR1, the HCDR3 includes an amino acid sequence as set forth in SEQ ID NO: 20, the HCDR2 includes an amino acid sequence as set forth in SEQ ID NO: 21, and the HCDR1 includes an amino acid sequence as set forth in SEQ ID NO: 22.

[0134] In some embodiments, the antibody or the antigen binding fragment thereof includes a LCDR3, a LCDR2, and a LCDR1, the LCDR3 includes an amino acid sequence as set forth in SEQ ID NO: 23, the LCDR2 includes an amino acid sequence as set forth in SEQ ID NO: 24, and the LCDR1 includes an amino acid sequence as set forth in SEQ ID NO: 25.

[0135] In some embodiments, the antibody or the antigen binding fragment thereof includes a HCDR3, a HCDR2, a HCDR1, a LCDR3, a LCDR2, and a LCDR1, the HCDR3 includes an amino acid sequence as set forth in SEQ ID NO: 20, the HCDR2 includes an amino acid sequence as set forth in SEQ ID NO: 21, the HCDR1 includes an amino acid sequence as set forth in SEQ ID NO: 22, the LCDR3 includes an amino acid sequence as set forth in SEQ ID NO: 23, the LCDR2 includes an amino acid sequence as set forth in SEQ ID NO: 24, and the LCDR1 includes an amino acid sequence as set forth in SEQ ID NO: 25.

[0136] In some embodiments, the antibody or the antigen binding fragment thereof includes a VH, and the VH includes an amino acid sequence as set forth in SEQ ID NO: 26. In some embodiments, the antibody or the antigen binding fragment thereof includes a VL, and the VL includes an amino acid sequence as set forth in SEQ ID NO: 27.

[0137] In some embodiments, the antibody or the antigen binding fragment thereof includes a VH and a VL, the VH includes an amino acid sequence as set forth in SEQ ID NO: 26 and the VL includes an amino acid sequence as set forth in SEQ ID NO: 27.

[0138] In some embodiments, the antibody or the antigen binding fragment thereof includes an amino acid sequence as set forth in SEQ ID NO: 28.

[0139] In some embodiments, the antibody targeting GPC-3 or the antigen binding fragment thereof includes a HCDR3, and the HCDR3 includes an amino acid sequence as set forth in SEQ ID NO: 29; in some embodiments, the antibody or the antigen binding fragment thereof includes a HCDR2, and the HCDR2 includes an amino acid sequence as set forth in SEQ ID NO: 30; in some embodiments, the antibody or the antigen binding fragment thereof includes a HCDR1, and the HCDR1 includes an amino acid sequence as set forth in SEQ ID NO: 31. In some embodiments, the

antibody or the antigen binding fragment thereof includes a LCDR3, and the LCDR3 includes an amino acid sequence as set forth in SEQ ID NO: 32; in some embodiments, the antibody or the antigen binding fragment thereof includes a LCDR2, and the LCDR2 includes an amino acid sequence as set forth in SEQ ID NO: 33; in some embodiments, the antibody or the antigen binding fragment thereof includes a LCDR1, and the LCDR1 includes an amino acid sequence as set forth in SEQ ID NO: 34.

[0140] In some embodiments, the antibody or the antigen binding fragment thereof includes a HCDR3, a HCDR2, and a HCDR1, the HCDR3 includes an amino acid sequence as set forth in SEQ ID NO: 29, the HCDR2 includes an amino acid sequence as set forth in SEQ ID NO: 30, and the HCDR1 includes an amino acid sequence as set forth in SEQ ID NO: 31.

[0141] In some embodiments, the antibody or the antigen binding fragment thereof includes a LCDR3, a LCDR2, and a LCDR1, the LCDR3 may include an amino acid sequence as set forth in SEQ ID NO: 32, the LCDR2 includes an amino acid sequence as set forth in SEQ ID NO: 33, and the LCDR1 includes an amino acid sequence as set forth in SEQ ID NO: 34.

[0142] In some embodiments, the antibody or the antigen binding fragment thereof includes a HCDR3, a HCDR2, a HCDR1, a LCDR3, a LCDR2, and a LCDR1, the HCDR3 includes an amino acid sequence as set forth in SEQ ID NO: 29, the HCDR2 includes an amino acid sequence as set forth in SEQ ID NO: 30, the HCDR1 includes an amino acid sequence as set forth in SEQ ID NO: 31, the LCDR3 includes an amino acid sequence as set forth in SEQ ID NO: 32, the LCDR2 includes an amino acid sequence as set forth in SEQ ID NO: 33, and the LCDR1 includes an amino acid sequence as set forth in SEQ ID NO: 34.

[0143] In some embodiments, the antibody or the antigen binding fragment thereof includes a VH, and the VH includes an amino acid sequence as set forth in SEQ ID NO: 35. In some embodiments, the antibody or the antigen binding fragment thereof includes a VL, and the VL includes an amino acid sequence as set forth in SEQ ID NO: 36.

[0144] In some embodiments, the antibody or the antigen binding fragment thereof includes a VH and a VL, the VH includes an amino acid sequence as set forth in SEQ ID NO: 35 and the VL includes an amino acid sequence as set forth in SEQ ID NO: 36.

[0145] In some embodiments, the antibody or the antigen binding fragment thereof includes an amino acid sequence as set forth in SEQ ID NO: 37.

[0146] In some embodiments, the antibody targeting GPC-3 or the antigen binding fragment thereof may include a HCDR3, and the HCDR3 includes an amino acid sequence as set forth in SEQ ID NO: 38; in some embodiments, the antibody or the antigen binding fragment thereof includes a HCDR2, and the HCDR2 includes an amino acid sequence as set forth in SEQ ID NO: 39; in some embodiments, the antibody or the antigen binding fragment thereof includes a HCDR1, and the HCDR1 includes an amino acid sequence as set forth in SEQ ID NO: 40. In some embodiments, the antibody or the antigen binding fragment thereof includes a LCDR3, and the LCDR3 includes an amino acid sequence as set forth in SEQ ID NO: 41; in some embodiments, the antibody or the antigen binding fragment thereof includes a LCDR2, and the LCDR2 includes an amino acid sequence as set forth in SEQ ID NO: 42; in some embodiments, the antibody or the antigen binding fragment thereof includes a LCDR1, and the LCDR1 includes an amino acid sequence as set forth in SEQ ID NO: 43.

[0147] In some embodiments, the antibody or the antigen binding fragment thereof includes a HCDR3, a HCDR2, and a HCDR1, the HCDR3 may include an amino acid sequence as set forth in SEQ ID NO: 38, the HCDR2 includes an amino acid sequence as set forth in SEQ ID NO: 39, and the HCDR1 includes an amino acid sequence as set forth in SEQ ID NO: 40.

[0148] In some embodiments, the antibody or the antigen binding fragment thereof includes a LCDR3, a LCDR2, and a LCDR1, the LCDR3 includes an amino acid sequence as set forth in SEQ ID NO: 41, the LCDR2 includes an amino acid sequence as set forth in SEQ ID NO: 42, and the LCDR1 includes an amino acid sequence as set forth in SEQ ID NO: 43.

[0149] In some embodiments, the antibody or the antigen binding fragment thereof includes a HCDR3, a HCDR2, a HCDR1, a LCDR3, a LCDR2, and a LCDR1, the HCDR3 includes an amino acid sequence as set forth in SEQ ID NO: 38, the HCDR2 includes an amino acid sequence as set forth in SEQ ID NO: 39, the HCDR1 includes an amino acid sequence as set forth in SEQ ID NO: 40, the LCDR3 includes an amino acid sequence as set forth in SEQ ID NO: 41, the LCDR2 includes an amino acid sequence as set forth in SEQ ID NO: 42, and the LCDR1 includes an amino acid sequence as set forth in SEQ ID NO: 43.

[0150] In some embodiments, the antibody or the antigen binding fragment thereof includes a VH, and the VH includes an amino acid sequence as set forth in SEQ ID NO: 44. In some embodiments, the antibody or the antigen binding fragment thereof includes a VL, and the VL includes an amino acid sequence as set forth in SEQ ID NO: 45.

[0151] In some embodiments, the antibody or the antigen binding fragment thereof includes a VH and a VL, the VH includes an amino acid sequence as set forth in SEQ ID NO: 44 and the VL includes an amino acid sequence as set forth in SEQ ID NO: 45.

[0152] In some embodiments, the antibody or the antigen binding fragment thereof includes an amino acid sequence as set forth in SEQ ID NO: 46.

[0153] In the present application, the antigen binding domain of the CAR may include an antibody specifically binding to CD20, CLDN18.2 or GPC-3 or an antigen binding fragment thereof. For example, the antibody of the present application or the antigen binding fragment thereof may include, but not limited to, a recombinant antibody, a monoclonal antibody, a human antibody, a humanized antibody, a chimeric antibody, a bispecific antibody, a single-chain antibody, a diabody, a triabody, a tetrabody, a Fv fragment, a scFv fragment, a Fab fragment, a Fab'fragment, a $F(ab')_2$ fragment.

[0154] In the present application, the antigen binding fragment may include Fab, Fab', $F(ab')_2$, F $(ab)_2$, a Fv fragment, scFv, di-scFv, and/or dAb.

[0155] In the present application, the antigen binding domain may be a single-chain antibody. For example, the CD20 binding domain is scFv. The scFv may include a sequence as set forth in SEQ ID NO: 10. For example, the CD20 binding domain may include the VH, VL and linking peptide of the antibody. For example, the linking peptide includes an amino acid sequence as set forth in SEQ ID NO: 9.

[0156] For example, the CLDN18.2 binding domain is scFv. The scFv may include a sequence as set forth in SEQ ID NO: 19. For example, the CLDN18.2 binding domain may include the VH, VL and linking peptide of the antibody. For example, the linking peptide includes an amino acid sequence as set forth in SEQ ID NO: 9.

[0157] For example, the GPC-3 binding domain is scFv. The scFv may include a sequence as set forth in SEQ ID NO: 28. For example, the GPC-3 binding domain may include the VH, VL and linking peptide of the antibody. For example, the linking peptide includes an amino acid sequence as set forth in SEQ ID NO: 9.

[0158] For example, the GPC-3 binding domain is scFv. The scFv may include a sequence as set forth in SEQ ID NO: 37. For example, the GPC-3 binding domain may include the VH, VL and linking peptide of the antibody. For example, the linking peptide includes an amino acid sequence as set forth in SEQ ID NO: 9.

[0159] For example, the GPC-3 binding domain is scFv. The scFv may include a sequence as set forth in SEQ ID NO: 46. For example, the GPC-3 binding domain may include the VH, VL and linking peptide of the antibody. For example, the linking peptide includes an amino acid sequence as set forth in SEQ ID NO: 9.

[0160] In the present application, the CAR may include a transmembrane domain, and the transmembrane domain may include a transmembrane domain of a protein selected from the group consisting of: CD28, CD3e, CD45, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137, and CD154. In some embodiments, the transmembrane domain includes an amino acid sequence as set forth in SEQ ID NO: 47.

[0161] In the present application, the CAR may include a co-stimulatory domain, and the co-stimulatory domain may include a co-stimulatory domain of a protein selected from the group consisting of: co-stimulatory signaling regions in CD28, 4-1BB, CD40L, TIM1, CD226, DR3, SLAM, ICOS, OX40, NKG2D, 2B4, CD244, FcεRIγ, BTLA, CD27, CD30, GITR, HVEM, DAP10, CD2, NKG2C, LIGHT, and DAP12. In some embodiments, the co-stimulatory domain includes a co-stimulatory domain of 4-1BB. In some embodiments, the co-stimulatory domain includes an amino acid sequence as set forth in SEQ ID NO: 48.

[0162] In the present application, the CAR may include an intracellular signaling domain, and the intracellular signaling domain may include a signaling domain derived from CD3. For example, the intracellular signaling domain may include an amino acid sequence as set forth in SEQ ID NO: 49.

[0163] In the present application, the CAR may include, sequentially from N-terminus to C-terminus, an antigen binding domain, a transmembrane domain, a co-stimulatory domain, and an intracellular signaling domain. For example, the antigen binding domain may include an amino acid sequence as set forth in SEQ ID NO: 10, SEQ ID NO: 19, SEQ ID NO: 28, SEQ ID NO: 37, or SEQ ID NO: 46, the transmembrane domain may include an amino acid sequence as set forth in SEQ ID NO: 47, the co-stimulatory domain may include an amino acid sequence as set forth in SEQ ID NO: 48, and the intracellular signaling domain may include an amino acid sequence as set forth in SEQ ID NO: 49.

[0164] In the present application, the CAR may further include a hinge region, by which the antigen binding domain and the transmembrane domain are linked. For example, the hinge region is derived from IgG family. For example, the hinge region is derived from IgG1. For example, the hinge region is derived from IgG4. For example, the hinge region is derived from IgD. For example, the hinge region is derived from CD8. For example, the hinge region may include an amino acid sequence as set forth in SEQ ID NO: 50.

[0165] In the present application, the CAR may be further linked to a signal peptide. For example, the signal peptide may be derived from CD8. For example, the signal peptide may be CD8a. The signal peptide is linked to the N-terminus of the antigen binding domain.

[0166] In the present application, the immune effector cell may further include and/or express a Bcl-2 protein or a functionally active fragment thereof. In some embodiments, the Bcl-2 protein or the functionally active fragment thereof includes an amino acid sequence as set forth in SEQ ID NO: 52.

[0167] In some embodiments, the Bcl-2 protein is introduced exogenously, for example, by adding a cleavage peptide and a sequence encoding the Bcl-2 protein or a functionally active fragment thereof to the nucleotide sequence encoding the chimeric antigen receptor, so that the Bcl-2 protein or the functionally active fragment thereof is expressed in the immune effector cell.

[0168] In some embodiments, for the modified immune effector cell, the modification of the immune effector cell includes making the immune effector cell include and/or express a chimeric antigen receptor and introducing an exogenous Bcl-2 protein or a functionally active fragment thereof into the immune effector cell.

[0169] In the present application, the functionally active fragment of Bcl-2 includes a fragment enabling the Bcl-2 protein to exert antiapoptotic function. For example, the functionally active fragment of Bcl-2 protein includes the BH4 domain thereof.

[0170] In some embodiments, the BBZ includes a hinge region, a transmembrane domain, a co-stimulatory domain, and an intracellular signaling domain.

[0171] In some embodiments, the 20BBZ includes a sequence of CAR targeting CD20. The 20BBZ includes an amino acid sequence as set forth in SEQ ID NO: 54. The 20BBZ-Bcl-2 includes sequences capable of expressing the CAR targeting CD20 and Bcl-2 protein or functionally active fragments thereof. The 20BBZ-Bcl-2 includes an amino acid sequence as set forth in SEQ ID NO: 53.

[0172] In some embodiments, the Ab10BBZ includes a sequence of CAR targeting CLDN18.2. The Ab10BBZ includes an amino acid sequence as set forth in SEQ ID NO: 56. The Ab10BBZ-Bcl-2 includes sequences capable of expressing the CAR targeting CLDN18.2 and Bcl-2 protein or functionally active fragments thereof. The Ab10BBZ-Bcl-2 includes an amino acid sequence as set forth in SEQ ID NO: 55.

[0173] In some embodiments, the GC33BBZ includes a sequence of CAR targeting GPC-3. The GC33BBZ includes an amino acid sequence as set forth in SEQ ID NO: 58. The GC33BBZ-Bcl-2 includes sequences capable of expressing the CAR targeting GPC-3 and Bcl-2 protein or functionally active fragments thereof. The GC33BBZ-Bcl-2 includes an amino acid sequence as set forth in SEQ ID NO: 57.

[0174] In some embodiments, the GC179BBZ includes a sequence of CAR targeting GPC-3. The GC179BBZ includes an amino acid sequence as set forth in SEQ ID NO:

60. The GC179BBZ-Bcl-2 includes sequences capable of expressing the CAR targeting GPC-3 and Bcl-2 protein or functionally active fragments thereof. The GC179BBZ-Bcl-2 includes an amino acid sequence as set forth in SEQ ID NO: 59.

[0175] In some embodiments, the M3C11BBZ includes a sequence of CAR targeting GPC-3. The M3C11BBZ includes an amino acid sequence as set forth in SEQ ID NO: 62. The M3C11BBZ-Bcl-2 includes sequences capable of expressing the CAR targeting GPC-3 and Bcl-2 protein or functionally active fragments thereof. The M3C11BBZ-Bcl-2 includes an amino acid sequence as set forth in SEQ ID NO: 61.

[0176] In the present application, the CAR includes an amino acid sequence as set forth in any one of SEQ ID NO: 53, SEQ ID NO: 55, SEQ ID NO: 57, SEQ ID NO: 59, and SEQ ID NO: 61.

[0177] Nucleic Acid Molecule, Vector, Cell, Preparation Method, Composition

[0178] In another aspect, the present application further provides one or more isolated nucleic acid molecules, which may encode the CAR of the present application. The one or more isolated nucleic acid molecules of the present application may be isolated nucleotides, deoxyribonucleotides or ribonucleotides of any length, or analogues thereof isolated from their natural environment or synthesized artificially, but they can encode the CAR of the present application.

[0179] In the present application, the nucleic acid molecules encode the chimeric antigen receptor and the Bcl-2 protein or the functionally active fragment thereof.

[0180] In the present application, the nucleic acid molecules also include a nucleotide sequence encoding the cleavage peptide. For example, the cleavage peptide may be 2A peptide. For example, the cleavage peptide may be selected from one or more of P2A, T2A, E2A, and F2A. For example, the cleavage peptide may include an amino acid sequence as set forth in SEQ ID NO: 51.

[0181] In some embodiments, the nucleic acid molecules include, sequentially from 5' end to 3' end, a sequence encoding the antigen binding domain, a sequence encoding the transmembrane domain, a sequence encoding the co-stimulatory domain, a sequence encoding the intracellular signaling domain, a sequence encoding the 2A peptide, and a sequence encoding the Bcl-2 protein or the functionally active fragment thereof.

[0182] For example, the nucleic acid molecules include, sequentially from 5' end to 3' end, nucleotide sequences encoding scFv targeting CD20, 4-1BB, CD3ζ, 2A, and Bcl-2. The nucleic acid sequences of the various moieties may be linked directly or indirectly. The indirect linkage may be through linkers.

[0183] For example, the nucleic acid molecules include, sequentially from 5' end to 3' end, nucleotide sequences encoding scFv targeting CLDN18.2, 4-1BB, CD3ζ, 2A, and Bcl-2. The nucleic acid sequences of the various moieties may be linked directly or indirectly. The indirect linkage may be through linkers.

[0184] For example, the nucleic acid molecules include, sequentially from 5' end to 3' end, nucleotide sequences encoding scFv targeting GPC-3, 4-1BB, CD3ζ, 2A, and Bcl-2. The nucleotide sequences of the various moieties may be linked directly or indirectly. The indirect linkage may be through linkers. For example, the nucleotide sequence encoding the scFv targeting GPC-3 may be the nucleotide sequence encoding GC33 scFv, GC179 scFv or M3C11scFv as provided in the embodiments.

[0185] In another aspect, the present application further provides a vector which may include the nucleic acid molecule of the present application. The vector can make the genetic elements it carries be expressed in a host cell by transforming, transducing or transfecting the host cell. For example, the vector may include plasmids; phagemids; Cosmids; artificial chromosomes, such as yeast artificial chromosomes (YACs), bacterial artificial chromosomes (BACs) or P1-derived artificial chromosomes (PACs); phages, such as lambda phages or M13 phages and animal viruses, and the like. The species of animal viruses used as the vector are retrovirus (including lentivirus), adenovirus, adeno-associated virus, herpes virus (e.g., herpes simplex virus), poxvirus, baculovirus, papilloma virus, papovavirus (e.g., SV40). Further for example, the vector may contain various elements for controlling the expression, including promoter sequences, transcription initiation sequences, enhancer sequences, selective elements, and reporter genes. In addition, the vector may also contain replication initiation sites. Moreover, the vector may also include ingredients that help its entry into cells, such as virion, lipidosome, or protein coat, but not only these substances. For example, the vector of the present application may be selected from one or more of plasmids, retroviral vectors, and lentiviral vectors. For example, the vector of the present application may be lentiviral vectors.

[0186] In another aspect, the present application further provides an immune effector cell, which may include the nucleic acid molecule of the present application or the vector of the present application. The cells may include the progeny of a single cell. Due to natural, accidental, or intentional mutations, the progeny may not necessarily be exactly the same as the original parent cells (in the form of the total DNA complement or in the genome). For example, the cells may also be mammal cells. In some embodiments, the immune effector cells also include T lymphocytes, such as α/β T lymphocytes and γ/δ T lymphocytes. For example, the immune effector cells may be derived from human PBMCs. For example, the T lymphocytes may be CD4+T cells or CD8+T cells. In some embodiments, the immune effector cells include natural killer cells, natural killer T cells, mastocytes, and bone marrow-derived phagocytes.

[0187] In another aspect, the present application further provides a method for preparing the immune effector cell of the present application, which may include introducing the isolated nucleic acid molecule of the present application or the vector of the present application into the immune effector cell.

[0188] In another aspect, the present application further provides a composition, which may include the immune effector cell of the present application. In some embodiments, the composition also includes a optionally pharmaceutically acceptable carrier.

[0189] In some embodiments, the acceptable ingredients of the composition may be non-toxic to the recipient at the dosage and concentration used. The pharmaceutical composition of the present application includes, but not limited to, liquid, frozen and freeze-dried compositions.

[0190] In some embodiments, the pharmaceutically acceptable adjuvant includes any and all solvents, dispersion media, isotonic agents, and absorption delaying agents that

are compatible with the immune effector cell, which are generally safe, non-toxic and neither biologically nor otherwise undesirable.

[0191] In some embodiments, the composition is administered parenterally, transdermally, intraperitoneally, intraarterially, intrathecally and/or intranasally or directly injected into tissues. For example, the composition may be administered to patients or subjects by means of infusion or injection. In some embodiments, the administration of the pharmaceutical composition can be carried out in different ways, such as intravenous, intraperitoneal, subcutaneous, intramuscular, topical, or intradermal administration. In some embodiments, the composition is administered incessantly. The incessant (or continuous) administration can be achieved by a small pump system worn by the patient to measure the therapeutic agent flowing into the patient, as described in WO2015/036583.

[0192] Use and Application

[0193] In another aspect, the present application further provides use of the immune effector cell, the nucleic acid molecule, the vector, the composition in the preparation of drugs for preventing and/or treating diseases and/or disorders.

[0194] In another aspect, the present application further provides a method for preventing and/or treating diseases and/or disorders, the method may include administering to a subject in need the immune effector cell or composition of the present application.

[0195] In the present application, the subject may include human and non-human animals. For example, the subject may include, but not limited to, cat, dog, horse, pig, cow, sheep, rabbit, mouse, rat, or monkey.

[0196] In another aspect, the immune effector cell of the present application, the nucleic acid molecule of the present application, the vector of the present application and/or the composition of the present application, they may be used for preventing, relieving or treating tumors.

[0197] In some embodiments, the diseases and/or disorders are associated with the expression of CD20.

[0198] In some embodiments, the diseases and/or disorders are associated with the expression of CLDN18.2.

[0199] In some embodiments, the diseases and/or disorders are associated with the expression of GPC-3.

[0200] In some embodiments, the diseases and/or disorders include tumors.

[0201] In some embodiments, the tumors include solid tumors and/or blood tumors.

[0202] In some embodiments, the tumors include CD20 positive tumors.

[0203] In some embodiments, the tumors include CLDN18.2 positive tumors.

[0204] In some embodiments, the tumors include GPC-3 positive tumors.

[0205] In some embodiments, the tumors include lymphoma.

[0206] In some embodiments, the tumors include pancreatic cancer.

[0207] Without intending to be limited by any theory, the embodiments below are intended only to illustrate the immune effector cell, the preparation method and the use of the present application and are not intended to limit the inventive scope of the present application.

EMBODIMENTS

Embodiment 1. Preparation of Anti-CD20 CAR-T Cells, Anti-CLDN18.2 CAR-T Cells, and Anti-GPC-3 CAR-T Cells

[0208] CAR targeting CD20 (20BBZ), CAR targeting CLDN18.2 (Ab10BBZ) and CARs targeting GPC-3 (GC33BBZ, GC179BBZ and M3C11BBZ) were prepared, wherein the structures of the CARs were as shown in FIG. **1**. The following sequences were artificially synthesized: scFv 20, scFv Abl 0, scFv GC33, scFv GC179, scFv M3C11, a hinge region, a transmembrane domain, a 4-1BB costimulatory domain, a CD3 intracellular signaling domain. Of those, BBZ can be obtained by connecting the hinge region, the transmembrane domain, the 4-1BB costimulatory domain and the CD3 intracellular signaling domain end to end. To both ends of scFv 20 which specifically binds to CD20, scFv Abl 0 which specifically binds to CLDN18.2, scFv GC33, scFv GC179 and scFv M3C11 which specifically bind to GPC-3, and BBZ was added XbaI and BamHI restriction sites to clone pCDH-MSCVEF vectors by overlap PCR. PCR amplification was performed, and to the 5' end was added XbaI restriction sites (containing protected bases), scFv 20/scFv Ab10/scFv GC33/scFv scFv GC179/scFv M3C11, a hinge region, a transmembrane domain, a 4-1BB costimulatory domain, a CD3 intracellular signaling domain, and a BamHI restriction site by extension PCR so that the PCR amplification resulted in the CARs: 20BBZ, Ab10BBZ, GC33BBZ, GC179BBZ and M3C11BBZ.

[0209] Viruses containing anti-CD20 CAR (20BBZ viruses), viruses containing anti-CLDN18.2 CAR (Ab10BBZ viruses) and viruses containing anti-GPC-3 CAR (GC33BBZ viruses, GC179BBZ viruses and M3C11BBZ viruses) were prepared. The correctly sequenced clones were subjected to non-endotoxin extraction with NucleoBond Xtra Midi Plus EF Kit and used to co-transfect 293 cells along with lentivirus packaging plasmids (VSV-g, pMD Gag/Pol or RSV-REV). After culture at 37° C., 5% CO_2 for 48 hrs., the supernatant was collected, filtered at 0.45 μM, and centrifuged at 25,000 RPM using Beckman Ultra-Centrifuge and SW28 Rotor for 2 hrs. to concentrate the viruses, that are viruses containing pCDH-MSCVEF-20BBZ, viruses containing pCDH-MSCVEF-Ab10BBZ, viruses containing pCDH-MSCVEF-GC33BBZ, viruses containing pCDH-MSCVEF-GC179BBZ and viruses containing pCDH-MSCVEF-M3C11BBZ (abbreviated as 20BBZ viruses, Ab10BBZ viruses, GC33BBZ viruses, GC179BBZ viruses, and M3C11BBZ viruses) for use in subsequent production of CAR-T cells. 293 cells were infected by the resultant viruses and detected by flow cytometry using anti-mouse Fab antibodies (Jackson ImmunoResearch #115-605-006) for virus titer. FIG. **2** shows the results of flow cytometry by adding 1 μL, 3 μL or 9 μL of the viruses, with no virus added as blank control. The results show that the CAR expression levels of CARs: 20BBZ, Ab10BBZ, GC33BBZ, GC179BBZ and M3C11BBZ increase with the increase of added virus doses.

[0210] Anti-CD20 CAR-T cells (20BBZ CAR-T cells), anti-CLDIN18.2CAR-T cells (Ab10BBZ CAR-T cells) and anti-GPC-3CAR-T cells (GC33BBZ CAR-T cells, GC179BBZ CAR-T cells and M3C11BBZ CAR-T cells) were prepared. Human PBMCs were purified by Stemcell T cell isolation kit (purchased from stem cell Catlog #19671), and then inoculated into 96-well plates coated with anti-

hCD3 (purchased from Bioxcell #BE0001-2) and anti-hCD28 (purchased from Bioxcell #BE0248). After 2 days, the cells were infected with the 20BBZ viruses, Ab10BBZ viruses, GC33BBZ viruses, GC179BBZ viruses and M3C11BBZ viruses prepared in this Embodiment at MOI (multiplicity of infection, i.e., a ratio of virus amount to cell number)=10-20. After 1 day, the cell culture was continued by replacing the medium, and the medium was 10% FBS-containing RPMI complete medium, IL2 (50 IU/ml), and IL21 (4 ng/ml). The culture was stimulated by artificial antigen-presenting cells (Raji-CLDN18.2 cells irradiated by X-ray at 100 Gray) or anti-hCD3 (0.1 μg/ml) or anti-hCD28 (0.25 μg/ml) every 6 days. After 2 rounds of stimulation, the resultant cells were 20BBZ CAR-T cells, Ab10BBZ CAR-T cells, GC33BBZ CAR-T cells, GC179BBZ CAR-T cells and M3C11BBZ CAR-T cells. By using Alexa Fluor® 647 AffiniPure F(ab')2 Fragment Goat Anti-Mouse IgG, Fab fragment specific antibody staining and flow cytometry, the results are shown in FIG. **3**. The results show that the resultant cells are all CAR-positive.

Embodiment 2. Preparation of Anti-CD20 Bcl-2 CAR-T Cells, Anti-CLDN18.2 Bcl-2 CAR-T Cells and Anti-GPC-3 Bcl-2 CAR-T Cells

[0211] Bcl-2-expressing CAR targeting CD20 (20BBZ-Bcl-2, with structure shown in FIG. **1**), CAR targeting CLDN18.2 (Ab10BBZ-Bcl-2, with structure shown in FIG. **1**), CARs targeting GPC-3 (GC33BBZ-Bcl-2, GC179BBZ-Bcl-2 and M3C11BBZ-Bcl-2, with structures shown in FIG. **1**), and Bcl-2-expressing anti-CD20 CAR-T viruses (20BBZ-Bcl-2 viruses), anti-CLDN18.2 CAR-T viruses (Ab10BBZ-Bcl-2 viruses), and anti-GPC-3 CAR-T viruses (GC33BBZ-Bcl-2 viruses, GC179BBZ-Bcl-2 viruses and M3C11BBZ-Bcl-2 viruses) were prepared in accordance with the method of Embodiment 1.

[0212] The 20BBZ, Ab10BBZ, GC33BBZ, GC179BBZ and M3C11BBZ were subjected to stop codon removal, and ligated to fragments of 2A, Bcl-2, and then subjected to overlap PCR, molecular cloning, and virus production to give pCDH-MSCVEF-20BBZ-Bcl-2 viruses, pCDH-MSCVEF-Ab10BBZ-Bcl-2 viruses, pCDH-MSCVEF-GC33BBZ-Bcl-2 viruses, pCDH-MSCVEF-GC179BBZ-Bcl-2 viruses, and pCDH-MSCVEF-M3C11BBZ-Bcl-2 viruses (abbreviated as 20BBZ-Bcl-2 viruses, Ab10BBZ-Bcl-2 viruses, GC33BBZ-Bcl-2 viruses, GC179BBZ-Bcl-2 viruses and M3C11BBZ-Bcl-2 viruses). The virus titer was detected by flow cytometry as in Embodiment 1. FIG. **2** shows the results of flow cytometry by adding 1 μL, 3 μL or 9 μL of the viruses, with no virus added as blank control. The results show that the CAR expression levels of the CARs: 20BBZ-Bcl-2, Ab10BBZ-Bcl-2, GC33BBZ-Bcl-2, GC179BBZ-Bcl-2, and M3C11BBZ-Bcl-2 increase with the increase of added virus doses.

[0213] Bcl-2-expressing anti-CD20 CAR-T cells (20BBZ-Bcl-2 CAR-T cells), anti-CLDIN18.2 CAR-T cells (Ab10BBZ-Bcl-2 CAR-T cells) and anti-GPC-3CAR-T cells (GC33BBZ-Bcl-2 CAR-T cells, GC179BBZ-Bcl-2 CAR-T cells and M3C11BBZ-Bcl-2 CAR-T cells) were prepared. Human PBMC-derived T cells were purified, activated, infected with 20BBZ-Bcl-2 viruses, Ab10BBZ-Bcl-2 viruses, GC33BBZ-Bcl-2 viruses, GC179BBZ-Bcl-2 viruses, M3C11BBZ-Bcl-2 viruses, and amplified to give 20BBZ-Bcl-2 CAR-T cells, Ab10BBZ-Bcl-2 CAR-T cells, GC33BBZ-Bcl-2 CAR-T cells, GC179BBZ-Bcl-2 CAR-T cells and M3C11BBZ-Bcl-2 CAR-T cells, respectively, which were stained with Alexa Fluor® 647 AffiniPure $F(ab)_2$ Fragment Goat Anti-Mouse IgG, Fab fragment specific antibodies by flow cytometry, with the results shown in FIG. **3**. The results show that the resultant cells are all CAR positive.

Embodiment 3. Expansion Ability of Anti-CD20 Bcl-2 CAR-T Cells

[0214] The CD20BBZ CAR-T cells prepared in Embodiment 1 and the CD20BBZ-Bcl-2 CAR-T cells prepared in Embodiment 2 were continuously cultured and stimulated with artificial antigen-presenting cells every 6 days. The cells were counted, with the results shown in FIG. **4**. It can be seen from FIG. **4** that the CD20BBZ-Bcl-2 CAR-T cells have better expansion ability as compared with the CD20BBZ CAR-T cells.

Embodiment 4. Expansion Ability of Anti-CLDN18.2 Bcl-2 CAR-T Cells

[0215] The Ab10BBZ CAR-T cells prepared in Embodiment 1 and the Ab10BBZ-Bcl-2 CAR-T cells prepared in Embodiment 2 were continuously cultured and stimulated with artificial antigen-presenting cells every 6 days. The cells were counted, with the results shown in FIG. **5**. It can be seen from FIG. **5** that the Ab10BBBZ-Bcl-2 CAR-T cells have better in vitro expansion ability as compared with the Ab10BBZ CAR-T cells.

Embodiment 5. Expansion Ability of Anti-GPC-3 Bcl-2 CAR-T Cells

[0216] The GC33BBZ CAR-T cells prepared in Embodiment 1 and the GC33BBZ-Bcl-2 CAR-T cells prepared in Embodiment 2 were continuously cultured and stimulated with artificial antigen-presenting cells every 6 days. The cells were counted, with the results shown in FIG. **6**. It can be seen from FIG. **6** that the GC33BBZ-Bcl-2 CAR-T cells have better in vitro expansion ability as compared with the GC33BBZ CAR-T cells.

Embodiment 6. In Vitro Tumor Killing Ability of Anti-CD20 Bcl-2 CAR-T Cells

[0217] The 20BBZ CAR-T cells prepared in Embodiment 1 and the 20BBZ-Bcl-2 CAR-T cells prepared in Embodiment 2 were inoculated into 96-well plates, and CD20-positive tumor cells (Raji) were added at a CAR-T: tumor cell ratio of 1:1, 0.5:1, and 0.25:1. After 24 hrs., the survival of Raji was detected by flow cytometer. As show in the detection of in vitro tumor killing effect in FIG. **7**, the 20BBZ-Bcl-2 CAR-T cells have a similar in vitro tumor killing ability as the 20BBZ CAR-T cells.

Embodiment 7. In Vivo Tumor Killing Ability of Anti-CD20 Bcl-2 CAR-T Cells

[0218] 3×10^6 Raji cells were inoculated into B-NDG mice by intravenous injection. After 6 days, the mice were administered with 10^7 CD20BBZ CAR-T cells or CD20BBZ-Bcl-2 CAR-T cells for treatment, and PBS was given as blank control. The ratio of T cells to Raji cells in the bone marrow of mice was measured, with the results shown in FIG. **8**A, respectively. In the bone marrow, the ratio of CD20BBZ-Bcl-2 CAR-T cells to CD20BBZ CAR-T cells

was significantly statistically different (P<0.01). As compared with the control group of CD20BBZ CAR-T cell treatment, the CD20BBZ-Bcl-2 CAR-T cell treatment significantly reduced the proportion of Raji cells in the bone marrow, which was significantly statistically different (P<0.001).

[0219] 3×10^6 Raji cells were inoculated into B-NDG mice by intravenous injection. After 6 days, the mice were administered with 10^7 CD20BBZ CAR-T cells or CD20BBZ-Bcl-2 CAR-T cells for treatment, and PBS was given as blank control. The survival curve of mice was plotted, with the results shown in FIG. **8**B. As compared with the control group of CD20BBZ CAR-T cell treatment, the mice treated with CD20BBZ-Bcl-2 CAR-T cells had a longer survival time of up to 48 days, demonstrating that the CD20BBZ-Bcl-2 CAR-T cells have significant anti-tumor ability in vitro.

Embodiment 8. In Vivo Tumor Killing Ability of Anti-CLDN18.2 Bcl-2 CAR-T Cells

[0220] 3×10^6 CFPAC-1 tumor cells were subcutaneously inoculated into B-NDG mice. After 6 days, the mice were administered with 10^7 Ab10BBZ CAR-T cells or Ab10BBZ-Bcl-2 CAR-T cells for treatment. The mice were measured for tumor load, with the results shown in FIG. **9**. As compared with Ab10BBZ CAR-T cells, the Ab10BBZ-Bcl-2 CAR-T cells can control the tumor load better. The results show that the tumor of mice treated with Ab10BBZ-Bcl-2 CAR-T cells began to shrink on Day 16, while the control tumor treated with Ab10BBZ CAR-T cells kept growing rapidly, demonstrating that the Ab10BBZ-Bcl-2 CAR-T cells had obvious anti-tumor ability in vivo.

Embodiment 9. In Vivo Tumor Killing Ability of Anti-GPC-3 Bcl-2 CAR-T Cells

[0221] 3×10^6 Huh-7 tumor cells were subcutaneously inoculated into B-NDG mice. After 7 days, the mice were administered with 10^7 GC33BBZ CAR-T cells or GC33BBZ-Bcl-2 CAR-T cells for treatment. The mice were measured for tumor load, with the results shown in FIG. **10**. As compared with GC33BBZ CAR-T cells, the GC33BBZ-Bcl-2 CAR-T cells can control the tumor load better and inhibit the tumor growth, demonstrating that the GC33BBZ-Bcl-2 CAR-T cells had obvious anti-tumor ability in vivo.

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<400> SEQUENCE: 5

Pro Trp Ile Tyr Ala Thr Ser Asn Leu Ala Ser
1 5 10

<210> SEQ ID NO 6
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: scFv20 LCDR1

<400> SEQUENCE: 6

Ser Ser Val Ser Tyr Ile His
1 5

<210> SEQ ID NO 7
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: scFv20 VH

<400> SEQUENCE: 7

Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Asn Met His Trp Val Lys Gln Thr Pro Gly Arg Gly Leu Glu Trp Ile
35 40 45

Gly Ala Ile Tyr Pro Gly Asn Gly Asp Thr Ser Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ser Thr Tyr Tyr Gly Gly Asp Trp Tyr Phe Asn Val Trp Gly
100 105 110

Ala Gly Thr Thr Val Thr Val Ser Ala
115 120

<210> SEQ ID NO 8
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: scFv20 VL

<400> SEQUENCE: 8

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Gln Ile Val Leu Ser Gln Ser Pro Ala Ile Leu Ser Ala Ser Pro Gly
1               5                   10                  15

Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Ser Val Ser Tyr Ile
            20                  25                  30

His Trp Phe Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp Ile Tyr
        35                  40                  45

Ala Thr Ser Asn Leu Ala Ser Gly Val Pro Val Arg Phe Ser Gly Ser
    50                  55                  60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Val Glu Ala Glu
65                  70                  75                  80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Thr Ser Asn Pro Pro Thr
                85                  90                  95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105


<210> SEQ ID NO 9
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: linker

<400> SEQUENCE: 9

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1               5                   10                  15


<210> SEQ ID NO 10
<211> LENGTH: 242
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: scFv20

<400> SEQUENCE: 10

Gln Ile Val Leu Ser Gln Ser Pro Ala Ile Leu Ser Ala Ser Pro Gly
1               5                   10                  15

Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Ser Val Ser Tyr Ile
            20                  25                  30

His Trp Phe Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp Ile Tyr
        35                  40                  45

Ala Thr Ser Asn Leu Ala Ser Gly Val Pro Val Arg Phe Ser Gly Ser
    50                  55                  60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Val Glu Ala Glu
65                  70                  75                  80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Thr Ser Asn Pro Pro Thr
                85                  90                  95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser Gly
            100                 105                 110

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Gln Gln Pro
        115                 120                 125

Gly Ala Glu Leu Val Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys
    130                 135                 140

Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Asn Met His Trp Val Lys Gln
145                 150                 155                 160

Thr Pro Gly Arg Gly Leu Glu Trp Ile Gly Ala Ile Tyr Pro Gly Asn
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               165                 170                 175

Gly Asp Thr Ser Tyr Asn Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr
            180                 185                 190

Ala Asp Lys Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr
        195                 200                 205

Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg Ser Thr Tyr Tyr Gly
    210                 215                 220

Gly Asp Trp Tyr Phe Asn Val Trp Gly Ala Gly Thr Thr Val Thr Val
225                 230                 235                 240

Ser Ala


<210> SEQ ID NO 11
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: scFvAb10 HCDR3

<400> SEQUENCE: 11

Arg Val Tyr Tyr Gly Asn Ser Phe Ala Tyr
1               5                   10


<210> SEQ ID NO 12
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: scFvAb10 HCDR2

<400> SEQUENCE: 12

Trp Ile Gly Leu Ile Asn Pro Gly Ser Gly Gly Thr Asn Tyr
1               5                   10


<210> SEQ ID NO 13
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: scFvAb10 HCDR1

<400> SEQUENCE: 13

Tyr Ala Phe Ser Asn Tyr Leu Ile Glu
1               5


<210> SEQ ID NO 14
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: scFvAb10 LCDR3

<400> SEQUENCE: 14

Gln Asn Asp Tyr Phe Tyr Pro Phe
1               5


<210> SEQ ID NO 15
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: scFvAb10 LCDR2
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<400> SEQUENCE: 15

Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser
1 5 10

<210> SEQ ID NO 16
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: scFvAb10 LCDR1

<400> SEQUENCE: 16

Gln Ser Leu Leu Asn Ser Gly Asn Gln Lys Asn Tyr Leu Thr
1 5 10

<210> SEQ ID NO 17
<211> LENGTH: 118
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: scFvAb10 VH

<400> SEQUENCE: 17

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Asn Tyr
20 25 30

Leu Ile Glu Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Leu Ile Asn Pro Gly Ser Gly Gly Thr Asn Tyr Asn Glu Lys Phe
50 55 60

Lys Gly Lys Ala Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Val Tyr Tyr Gly Asn Ser Phe Ala Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> SEQ ID NO 18
<211> LENGTH: 116
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: scFvAb10 VL

<400> SEQUENCE: 18

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

Gly Asn Gln Lys Asn Tyr Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

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Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Asn
85 90 95

Asp Tyr Phe Tyr Pro Phe Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
100 105 110

Lys Arg Thr Val
115

<210> SEQ ID NO 19
<211> LENGTH: 249
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: scFvAb10

<400> SEQUENCE: 19

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

Gly Asn Gln Lys Asn Tyr Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Asn
85 90 95

Asp Tyr Phe Tyr Pro Phe Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
100 105 110

Lys Arg Thr Val Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
115 120 125

Gly Gly Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
130 135 140

Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ala Phe
145 150 155 160

Ser Asn Tyr Leu Ile Glu Trp Val Lys Gln Ala Pro Gly Gln Gly Leu
165 170 175

Glu Trp Ile Gly Leu Ile Asn Pro Gly Ser Gly Gly Thr Asn Tyr Asn
180 185 190

Glu Lys Phe Lys Gly Lys Ala Thr Ile Thr Ala Asp Lys Ser Thr Ser
195 200 205

Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
210 215 220

Tyr Tyr Cys Ala Arg Val Tyr Tyr Gly Asn Ser Phe Ala Tyr Trp Gly
225 230 235 240

Gln Gly Thr Leu Val Thr Val Ser Ser
245

<210> SEQ ID NO 20
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: scFvGC33 HCDR3

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<400> SEQUENCE: 20

Thr Arg Phe Tyr Ser Tyr Thr Tyr
1 5

<210> SEQ ID NO 21
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: scFvGC33 HCDR2

<400> SEQUENCE: 21

Trp Met Gly Ala Leu Asp Pro Lys Thr Gly Asp Thr Ala Tyr
1 5 10

<210> SEQ ID NO 22
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: scFvGC33 HCDR1

<400> SEQUENCE: 22

Tyr Thr Phe Thr Asp Tyr Glu Met His
1 5

<210> SEQ ID NO 23
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: scFvGC33 LCDR3

<400> SEQUENCE: 23

Ser Gln Asn Thr His Val Pro Pro
1 5

<210> SEQ ID NO 24
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: scFvGC33 LCDR2

<400> SEQUENCE: 24

Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser
1 5 10

<210> SEQ ID NO 25
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: scFvGC33 LCDR1

<400> SEQUENCE: 25

Gln Ser Leu Val His Ser Asn Ala Asn Thr Tyr Leu His
1 5 10

<210> SEQ ID NO 26
<211> LENGTH: 115
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: scFvGC33 VH

<400> SEQUENCE: 26

Gln Val Gln Leu Val Glu Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ala Leu Asp Pro Lys Thr Gly Asp Thr Ala Tyr Ser Gln Lys Phe
50 55 60

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> SEQ ID NO 27
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: scFvGC33 VL

<400> SEQUENCE: 27

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Ala Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Ser Gln Asn
85 90 95

Thr His Val Pro Pro Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> SEQ ID NO 28
<211> LENGTH: 242
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: scFvGC33

<400> SEQUENCE: 28

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Ala Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser

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        35                  40                  45

Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
    50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Ser Gln Asn
                85                  90                  95

Thr His Val Pro Pro Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln
        115                 120                 125

Val Gln Leu Val Glu Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Ser
    130                 135                 140

Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr Glu
145                 150                 155                 160

Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met Gly
                165                 170                 175

Ala Leu Asp Pro Lys Thr Gly Asp Thr Ala Tyr Ser Gln Lys Phe Lys
            180                 185                 190

Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr Met
        195                 200                 205

Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys Thr
    210                 215                 220

Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
225                 230                 235                 240

Ser Ser


<210> SEQ ID NO 29
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: scFvGC179 HCDR3

<400> SEQUENCE: 29

Arg Glu Val Thr Thr Ser Phe Ala Tyr
1               5


<210> SEQ ID NO 30
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: scFvGC179 HCDR2

<400> SEQUENCE: 30

Trp Val Ala Arg Ile Arg Ser Glu Ser Asn Asn Tyr Ala Thr Tyr Tyr
1               5                   10                  15

Gly


<210> SEQ ID NO 31
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: scFvGC179 HCDR1
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<400> SEQUENCE: 31

Phe Ser Phe Asn Ile Asn Ala Met Asn
1 5

<210> SEQ ID NO 32
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: scFvGC179 LCDR3

<400> SEQUENCE: 32

Met Gln His Ile Glu Tyr Pro Phe
1 5

<210> SEQ ID NO 33
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: scFvGC179 LCDR2

<400> SEQUENCE: 33

Leu Leu Ile Tyr Trp Met Ser Asn Leu Ala Ser
1 5 10

<210> SEQ ID NO 34
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: scFvGC179 LCDR1

<400> SEQUENCE: 34

Lys Ser Leu Leu His Ser Asn Gly Asn Thr Tyr Leu Asn
1 5 10

<210> SEQ ID NO 35
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: scFvGC179 VH

<400> SEQUENCE: 35

Glu Val Gln Leu Val Glu Thr Gly Gly Gly Leu Val Gln Pro Glu Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Asn Ile Asn
20 25 30

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Arg Ile Arg Ser Glu Ser Asn Asn Tyr Ala Thr Tyr Tyr Gly Asp
50 55 60

Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Gln Asn Met
65 70 75 80

Leu Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Ile Tyr
85 90 95

Tyr Cys Val Arg Glu Val Thr Thr Ser Phe Ala Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ala

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115

<210> SEQ ID NO 36
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: scFvGC179 VL

<400> SEQUENCE: 36

Asp Ile Val Met Thr Gln Ser Ala Pro Ser Val Pro Val Thr Pro Gly
1 5 10 15

Glu Ser Val Ser Ile Ser Cys Lys Ser Ser Lys Ser Leu Leu His Ser
20 25 30

Asn Gly Asn Thr Tyr Leu Asn Trp Phe Leu Gln Arg Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Trp Met Ser Asn Leu Ala Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Ala Phe Thr Leu Arg Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln His
85 90 95

Ile Glu Tyr Pro Phe Thr Phe Gly Thr Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> SEQ ID NO 37
<211> LENGTH: 246
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: scFvGC179

<400> SEQUENCE: 37

Asp Ile Val Met Thr Gln Ser Ala Pro Ser Val Pro Val Thr Pro Gly
1 5 10 15

Glu Ser Val Ser Ile Ser Cys Lys Ser Ser Lys Ser Leu Leu His Ser
20 25 30

Asn Gly Asn Thr Tyr Leu Asn Trp Phe Leu Gln Arg Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Trp Met Ser Asn Leu Ala Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Ala Phe Thr Leu Arg Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln His
85 90 95

Ile Glu Tyr Pro Phe Thr Phe Gly Thr Gly Thr Lys Leu Glu Ile Lys
100 105 110

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
115 120 125

Val Gln Leu Val Glu Thr Gly Gly Gly Leu Val Gln Pro Glu Gly Ser
130 135 140

Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Asn Ile Asn Ala
145 150 155 160

Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala
165 170 175

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Arg Ile Arg Ser Glu Ser Asn Asn Tyr Ala Thr Tyr Tyr Gly Asp Ser
180 185 190

Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Gln Asn Met Leu
195 200 205

Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Ile Tyr Tyr
210 215 220

Cys Val Arg Glu Val Thr Thr Ser Phe Ala Tyr Trp Gly Gln Gly Thr
225 230 235 240

Leu Val Thr Val Ser Ala
245

<210> SEQ ID NO 38
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: scFvM3C11 HCDR3

<400> SEQUENCE: 38

Val Arg Gln Gly Gly Ala Tyr
1 5

<210> SEQ ID NO 39
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: scFvM3C11 HCDR2

<400> SEQUENCE: 39

Trp Val Ala Ala Ile Asp Ser Ser Gly Gly Asp Thr Tyr Tyr Leu
1 5 10 15

<210> SEQ ID NO 40
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: scFvM3C11 HCDR1

<400> SEQUENCE: 40

Phe Thr Phe Ser Arg Tyr Ala Met Ser
1 5

<210> SEQ ID NO 41
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: scFvM3C11 LCDR3

<400> SEQUENCE: 41

Trp Gln Gly Thr His Phe Pro Leu
1 5

<210> SEQ ID NO 42
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: scFvM3C11 LCDR2

<400> SEQUENCE: 42

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Arg Leu Ile Tyr Leu Val Ser Lys Leu Asp Ser
1 5 10

<210> SEQ ID NO 43
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: scFvM3C11 LCDR1

<400> SEQUENCE: 43

Gln Ser Leu Leu Asp Ser Asp Gly Lys Thr Tyr Leu Asn
1 5 10

<210> SEQ ID NO 44
<211> LENGTH: 114
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: scFvM3C11 VH

<400> SEQUENCE: 44

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ile Pro Glu Lys Ile Leu Glu Trp Val
35 40 45

Ala Ala Ile Asp Ser Ser Gly Gly Asp Thr Tyr Tyr Leu Asp Thr Val
50 55 60

Lys Asp Arg Phe Thr Ile Ser Arg Asp Asn Ala Asn Asn Thr Leu His
65 70 75 80

Leu Gln Met Arg Ser Leu Arg Ser Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

Val Arg Gln Gly Gly Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
100 105 110

Ser Ala

<210> SEQ ID NO 45
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: scFvM3C11 VL

<400> SEQUENCE: 45

Asp Val Val Met Thr Gln Thr Pro Leu Thr Leu Ser Val Thr Ile Gly
1 5 10 15

Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Leu Leu Asp Ser
20 25 30

Asp Gly Lys Thr Tyr Leu Asn Trp Leu Leu Gln Arg Pro Gly Gln Ser
35 40 45

Pro Lys Arg Leu Ile Tyr Leu Val Ser Lys Leu Asp Ser Gly Ala Pro
50 55 60

Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Ile Tyr Tyr Cys Trp Gln Gly

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                85                  90                  95

Thr His Phe Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
            100                 105                 110


<210> SEQ ID NO 46
<211> LENGTH: 241
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: scFvM3C11

<400> SEQUENCE: 46

Asp Val Val Met Thr Gln Thr Pro Leu Thr Leu Ser Val Thr Ile Gly
1               5                   10                  15

Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Leu Leu Asp Ser
            20                  25                  30

Asp Gly Lys Thr Tyr Leu Asn Trp Leu Leu Gln Arg Pro Gly Gln Ser
        35                  40                  45

Pro Lys Arg Leu Ile Tyr Leu Val Ser Lys Leu Asp Ser Gly Ala Pro
    50                  55                  60

Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Leu Gly Ile Tyr Tyr Cys Trp Gln Gly
                85                  90                  95

Thr His Phe Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
            100                 105                 110

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
        115                 120                 125

Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly Ser
    130                 135                 140

Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr Ala
145                 150                 155                 160

Met Ser Trp Val Arg Gln Ile Pro Glu Lys Ile Leu Glu Trp Val Ala
                165                 170                 175

Ala Ile Asp Ser Ser Gly Gly Asp Thr Tyr Tyr Leu Asp Thr Val Lys
            180                 185                 190

Asp Arg Phe Thr Ile Ser Arg Asp Asn Ala Asn Asn Thr Leu His Leu
        195                 200                 205

Gln Met Arg Ser Leu Arg Ser Glu Asp Thr Ala Leu Tyr Tyr Cys Val
    210                 215                 220

Arg Gln Gly Gly Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
225                 230                 235                 240

Ala


<210> SEQ ID NO 47
<211> LENGTH: 24
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: transmembrane domain

<400> SEQUENCE: 47

Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu
1               5                   10                  15

Ser Leu Val Ile Thr Leu Tyr Cys
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<210> SEQ ID NO 48
<211> LENGTH: 42
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: co-stimulatory domain

<400> SEQUENCE: 48

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
1 5 10 15

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
20 25 30

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu
35 40

<210> SEQ ID NO 49
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: intracellular signaling domain

<400> SEQUENCE: 49

Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly
1 5 10 15

Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr
20 25 30

Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys
35 40 45

Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys
50 55 60

Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg
65 70 75 80

Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala
85 90 95

Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
100 105 110

<210> SEQ ID NO 50
<211> LENGTH: 45
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hinge region

<400> SEQUENCE: 50

Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala
1 5 10 15

Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly
20 25 30

Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp
35 40 45

<210> SEQ ID NO 51
<211> LENGTH: 22
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

-continued

<220> FEATURE:
<223> OTHER INFORMATION: 2A peptide

<400> SEQUENCE: 51

Gly Ser Gly Ala Thr Asn Phe Ser Leu Leu Lys Gln Ala Gly Asp Val
1 5 10 15

Glu Glu Asn Pro Gly Pro
20

<210> SEQ ID NO 52
<211> LENGTH: 239
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Bcl-2

<400> SEQUENCE: 52

Met Ala His Ala Gly Arg Thr Gly Tyr Asp Asn Arg Glu Ile Val Met
1 5 10 15

Lys Tyr Ile His Tyr Lys Leu Ser Gln Arg Gly Tyr Glu Trp Asp Ala
20 25 30

Gly Asp Val Gly Ala Ala Pro Pro Gly Ala Ala Pro Ala Pro Gly Ile
35 40 45

Phe Ser Ser Gln Pro Gly His Thr Pro His Pro Ala Ala Ser Arg Asp
50 55 60

Pro Val Ala Arg Thr Ser Pro Leu Gln Thr Pro Ala Ala Pro Gly Ala
65 70 75 80

Ala Ala Gly Pro Ala Leu Ser Pro Val Pro Pro Val Val His Leu Thr
85 90 95

Leu Arg Gln Ala Gly Asp Asp Phe Ser Arg Arg Tyr Arg Arg Asp Phe
100 105 110

Ala Glu Met Ser Ser Gln Leu His Leu Thr Pro Phe Thr Ala Arg Gly
115 120 125

Arg Phe Ala Thr Val Val Glu Glu Leu Phe Arg Asp Gly Val Asn Trp
130 135 140

Gly Arg Ile Val Ala Phe Phe Glu Phe Gly Gly Val Met Cys Val Glu
145 150 155 160

Ser Val Asn Arg Glu Met Ser Pro Leu Val Asp Asn Ile Ala Leu Trp
165 170 175

Met Thr Glu Tyr Leu Asn Arg His Leu His Thr Trp Ile Gln Asp Asn
180 185 190

Gly Gly Trp Asp Ala Phe Val Glu Leu Tyr Gly Pro Ser Met Arg Pro
195 200 205

Leu Phe Asp Phe Ser Trp Leu Ser Leu Lys Thr Leu Leu Ser Leu Ala
210 215 220

Leu Val Gly Ala Cys Ile Thr Leu Gly Ala Tyr Leu Gly His Lys
225 230 235

<210> SEQ ID NO 53
<211> LENGTH: 751
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 20BBZ-Bcl-2

<400> SEQUENCE: 53

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```
Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1               5                  10                  15

Gly Ser Thr Gly Thr Gly Gln Ile Val Leu Ser Gln Ser Pro Ala Ile
            20                  25                  30

Leu Ser Ala Ser Pro Gly Glu Lys Val Thr Met Thr Cys Arg Ala Ser
        35                  40                  45

Ser Ser Val Ser Tyr Ile His Trp Phe Gln Gln Lys Pro Gly Ser Ser
    50                  55                  60

Pro Lys Pro Trp Ile Tyr Ala Thr Ser Asn Leu Ala Ser Gly Val Pro
65                  70                  75                  80

Val Arg Phe Ser Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile
                85                  90                  95

Ser Arg Val Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp
            100                 105                 110

Thr Ser Asn Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln
    130                 135                 140

Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Pro Gly Ala Ser
145                 150                 155                 160

Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Asn
                165                 170                 175

Met His Trp Val Lys Gln Thr Pro Gly Arg Gly Leu Glu Trp Ile Gly
            180                 185                 190

Ala Ile Tyr Pro Gly Asn Gly Asp Thr Ser Tyr Asn Gln Lys Phe Lys
        195                 200                 205

Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr Met
    210                 215                 220

Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala
225                 230                 235                 240

Arg Ser Thr Tyr Tyr Gly Gly Asp Trp Tyr Phe Asn Val Trp Gly Ala
                245                 250                 255

Gly Thr Thr Val Thr Val Ser Ala Ala Ala Ala Thr Thr Thr Pro Ala
            260                 265                 270

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser
        275                 280                 285

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr
    290                 295                 300

Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala
305                 310                 315                 320

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
                325                 330                 335

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
            340                 345                 350

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
        355                 360                 365

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg
    370                 375                 380

Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn
385                 390                 395                 400

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
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               405                 410                 415

Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro
            420                 425                 430

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
        435                 440                 445

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
    450                 455                 460

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
465                 470                 475                 480

Ala Leu His Met Gln Ala Leu Pro Pro Arg Gly Ser Gly Ala Thr Asn
                485                 490                 495

Phe Ser Leu Leu Lys Gln Ala Gly Asp Val Glu Glu Asn Pro Gly Pro
            500                 505                 510

Met Ala His Ala Gly Arg Thr Gly Tyr Asp Asn Arg Glu Ile Val Met
        515                 520                 525

Lys Tyr Ile His Tyr Lys Leu Ser Gln Arg Gly Tyr Glu Trp Asp Ala
    530                 535                 540

Gly Asp Val Gly Ala Ala Pro Pro Gly Ala Ala Pro Ala Pro Gly Ile
545                 550                 555                 560

Phe Ser Ser Gln Pro Gly His Thr Pro His Pro Ala Ala Ser Arg Asp
                565                 570                 575

Pro Val Ala Arg Thr Ser Pro Leu Gln Thr Pro Ala Ala Pro Gly Ala
            580                 585                 590

Ala Ala Gly Pro Ala Leu Ser Pro Val Pro Pro Val Val His Leu Thr
        595                 600                 605

Leu Arg Gln Ala Gly Asp Asp Phe Ser Arg Arg Tyr Arg Arg Asp Phe
    610                 615                 620

Ala Glu Met Ser Ser Gln Leu His Leu Thr Pro Phe Thr Ala Arg Gly
625                 630                 635                 640

Arg Phe Ala Thr Val Val Glu Glu Leu Phe Arg Asp Gly Val Asn Trp
                645                 650                 655

Gly Arg Ile Val Ala Phe Phe Glu Phe Gly Gly Val Met Cys Val Glu
            660                 665                 670

Ser Val Asn Arg Glu Met Ser Pro Leu Val Asp Asn Ile Ala Leu Trp
        675                 680                 685

Met Thr Glu Tyr Leu Asn Arg His Leu His Thr Trp Ile Gln Asp Asn
    690                 695                 700

Gly Gly Trp Asp Ala Phe Val Glu Leu Tyr Gly Pro Ser Met Arg Pro
705                 710                 715                 720

Leu Phe Asp Phe Ser Trp Leu Ser Leu Lys Thr Leu Leu Ser Leu Ala
                725                 730                 735

Leu Val Gly Ala Cys Ile Thr Leu Gly Ala Tyr Leu Gly His Lys
            740                 745                 750


<210> SEQ ID NO 54
<211> LENGTH: 490
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 20BBZ

<400> SEQUENCE: 54

Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
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```
1               5                   10                  15

Gly Ser Thr Gly Thr Gly Gln Ile Val Leu Ser Gln Ser Pro Ala Ile
            20                  25                  30

Leu Ser Ala Ser Pro Gly Glu Lys Val Thr Met Thr Cys Arg Ala Ser
        35                  40                  45

Ser Ser Val Ser Tyr Ile His Trp Phe Gln Gln Lys Pro Gly Ser Ser
    50                  55                  60

Pro Lys Pro Trp Ile Tyr Ala Thr Ser Asn Leu Ala Ser Gly Val Pro
65                  70                  75                  80

Val Arg Phe Ser Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile
                85                  90                  95

Ser Arg Val Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp
            100                 105                 110

Thr Ser Asn Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln
    130                 135                 140

Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Pro Gly Ala Ser
145                 150                 155                 160

Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Asn
                165                 170                 175

Met His Trp Val Lys Gln Thr Pro Gly Arg Gly Leu Glu Trp Ile Gly
            180                 185                 190

Ala Ile Tyr Pro Gly Asn Gly Asp Thr Ser Tyr Asn Gln Lys Phe Lys
        195                 200                 205

Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr Met
    210                 215                 220

Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala
225                 230                 235                 240

Arg Ser Thr Tyr Tyr Gly Gly Asp Trp Tyr Phe Asn Val Trp Gly Ala
                245                 250                 255

Gly Thr Thr Val Thr Val Ser Ala Ala Ala Ala Thr Thr Thr Pro Ala
            260                 265                 270

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser
        275                 280                 285

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr
    290                 295                 300

Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala
305                 310                 315                 320

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
                325                 330                 335

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
            340                 345                 350

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
        355                 360                 365

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg
    370                 375                 380

Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn
385                 390                 395                 400

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
                405                 410                 415
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Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro
            420                 425                 430

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
        435                 440                 445

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
    450                 455                 460

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
465                 470                 475                 480

Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490


<210> SEQ ID NO 55
<211> LENGTH: 758
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Ab10BBZ-Bcl-2

<400> SEQUENCE: 55

Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1               5                   10                  15

Gly Ser Thr Gly Thr Gly Asp Ile Val Met Thr Gln Ser Pro Asp Ser
            20                  25                  30

Leu Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Ser Cys Lys Ser Ser
        35                  40                  45

Gln Ser Leu Leu Asn Ser Gly Asn Gln Lys Asn Tyr Leu Thr Trp Tyr
    50                  55                  60

Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser
65                  70                  75                  80

Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly
                85                  90                  95

Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala
            100                 105                 110

Val Tyr Tyr Cys Gln Asn Asp Tyr Phe Tyr Pro Phe Thr Phe Gly Gln
        115                 120                 125

Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Val Gln Ser
145                 150                 155                 160

Gly Ala Glu Val Lys Lys Pro Gly Ser Ser Val Lys Val Ser Cys Lys
                165                 170                 175

Ala Ser Gly Tyr Ala Phe Ser Asn Tyr Leu Ile Glu Trp Val Lys Gln
            180                 185                 190

Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly Leu Ile Asn Pro Gly Ser
        195                 200                 205

Gly Gly Thr Asn Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Ile Thr
    210                 215                 220

Ala Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg
225                 230                 235                 240

Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Val Tyr Tyr Gly Asn
                245                 250                 255

Ser Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala
            260                 265                 270
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```
Ala Ala Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr
        275                 280                 285

Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala
    290                 295                 300

Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile
305                 310                 315                 320

Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser
                325                 330                 335

Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr
            340                 345                 350

Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu
        355                 360                 365

Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu
    370                 375                 380

Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln
385                 390                 395                 400

Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu
                405                 410                 415

Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly
            420                 425                 430

Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln
        435                 440                 445

Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu
    450                 455                 460

Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr
465                 470                 475                 480

Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro
                485                 490                 495

Arg Gly Ser Gly Ala Thr Asn Phe Ser Leu Leu Lys Gln Ala Gly Asp
            500                 505                 510

Val Glu Glu Asn Pro Gly Pro Met Ala His Ala Gly Arg Thr Gly Tyr
        515                 520                 525

Asp Asn Arg Glu Ile Val Met Lys Tyr Ile His Tyr Lys Leu Ser Gln
    530                 535                 540

Arg Gly Tyr Glu Trp Asp Ala Gly Asp Val Gly Ala Ala Pro Pro Gly
545                 550                 555                 560

Ala Ala Pro Ala Pro Gly Ile Phe Ser Ser Gln Pro Gly His Thr Pro
                565                 570                 575

His Pro Ala Ala Ser Arg Asp Pro Val Ala Arg Thr Ser Pro Leu Gln
            580                 585                 590

Thr Pro Ala Ala Pro Gly Ala Ala Ala Gly Pro Ala Leu Ser Pro Val
        595                 600                 605

Pro Pro Val Val His Leu Thr Leu Arg Gln Ala Gly Asp Asp Phe Ser
    610                 615                 620

Arg Arg Tyr Arg Arg Asp Phe Ala Glu Met Ser Ser Gln Leu His Leu
625                 630                 635                 640

Thr Pro Phe Thr Ala Arg Gly Arg Phe Ala Thr Val Val Glu Glu Leu
                645                 650                 655

Phe Arg Asp Gly Val Asn Trp Gly Arg Ile Val Ala Phe Phe Glu Phe
            660                 665                 670
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```
Gly Gly Val Met Cys Val Glu Ser Val Asn Arg Glu Met Ser Pro Leu
        675                 680                 685

Val Asp Asn Ile Ala Leu Trp Met Thr Glu Tyr Leu Asn Arg His Leu
    690                 695                 700

His Thr Trp Ile Gln Asp Asn Gly Gly Trp Asp Ala Phe Val Glu Leu
705                 710                 715                 720

Tyr Gly Pro Ser Met Arg Pro Leu Phe Asp Phe Ser Trp Leu Ser Leu
                725                 730                 735

Lys Thr Leu Leu Ser Leu Ala Leu Val Gly Ala Cys Ile Thr Leu Gly
            740                 745                 750

Ala Tyr Leu Gly His Lys
        755


<210> SEQ ID NO 56
<211> LENGTH: 497
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Ab10BBZ

<400> SEQUENCE: 56

Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1               5                   10                  15

Gly Ser Thr Gly Thr Gly Asp Ile Val Met Thr Gln Ser Pro Asp Ser
            20                  25                  30

Leu Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Ser Cys Lys Ser Ser
        35                  40                  45

Gln Ser Leu Leu Asn Ser Gly Asn Gln Lys Asn Tyr Leu Thr Trp Tyr
    50                  55                  60

Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser
65                  70                  75                  80

Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly
                85                  90                  95

Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala
            100                 105                 110

Val Tyr Tyr Cys Gln Asn Asp Tyr Phe Tyr Pro Phe Thr Phe Gly Gln
        115                 120                 125

Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Val Gln Ser
145                 150                 155                 160

Gly Ala Glu Val Lys Lys Pro Gly Ser Ser Val Lys Val Ser Cys Lys
                165                 170                 175

Ala Ser Gly Tyr Ala Phe Ser Asn Tyr Leu Ile Glu Trp Val Lys Gln
            180                 185                 190

Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly Leu Ile Asn Pro Gly Ser
        195                 200                 205

Gly Gly Thr Asn Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Ile Thr
    210                 215                 220

Ala Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg
225                 230                 235                 240

Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Val Tyr Tyr Gly Asn
                245                 250                 255
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Ser Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala
            260                 265                 270

Ala Ala Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr
        275                 280                 285

Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala
    290                 295                 300

Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile
305                 310                 315                 320

Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser
                325                 330                 335

Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr
            340                 345                 350

Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu
        355                 360                 365

Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu
    370                 375                 380

Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln
385                 390                 395                 400

Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu
                405                 410                 415

Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly
            420                 425                 430

Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln
        435                 440                 445

Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu
    450                 455                 460

Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr
465                 470                 475                 480

Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro
                485                 490                 495

Arg


<210> SEQ ID NO 57
<211> LENGTH: 751
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: GC33BBZ-Bcl-2

<400> SEQUENCE: 57

Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1               5                   10                  15

Gly Ser Thr Gly Thr Gly Asp Val Val Met Thr Gln Ser Pro Leu Ser
            20                  25                  30

Leu Pro Val Thr Pro Gly Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser
        35                  40                  45

Gln Ser Leu Val His Ser Asn Ala Asn Thr Tyr Leu His Trp Tyr Leu
    50                  55                  60

Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn
65                  70                  75                  80

Arg Phe Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr
                85                  90                  95

Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val
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            100                 105                 110

Tyr Tyr Cys Ser Gln Asn Thr His Val Pro Pro Thr Phe Gly Gln Gly
        115                 120                 125

Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
    130                 135                 140

Gly Gly Gly Gly Ser Gln Val Gln Leu Val Glu Ser Gly Ala Glu Val
145                 150                 155                 160

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
                165                 170                 175

Thr Phe Thr Asp Tyr Glu Met His Trp Val Arg Gln Ala Pro Gly Gln
            180                 185                 190

Gly Leu Glu Trp Met Gly Ala Leu Asp Pro Lys Thr Gly Asp Thr Ala
        195                 200                 205

Tyr Ser Gln Lys Phe Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser
    210                 215                 220

Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr
225                 230                 235                 240

Ala Val Tyr Tyr Cys Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln
                245                 250                 255

Gly Thr Leu Val Thr Val Ser Ser Ala Ala Ala Thr Thr Thr Pro Ala
            260                 265                 270

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser
        275                 280                 285

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr
    290                 295                 300

Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala
305                 310                 315                 320

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
                325                 330                 335

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
            340                 345                 350

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
        355                 360                 365

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg
    370                 375                 380

Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn
385                 390                 395                 400

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
                405                 410                 415

Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro
            420                 425                 430

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
        435                 440                 445

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
    450                 455                 460

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
465                 470                 475                 480

Ala Leu His Met Gln Ala Leu Pro Pro Arg Gly Ser Gly Ala Thr Asn
                485                 490                 495

Phe Ser Leu Leu Lys Gln Ala Gly Asp Val Glu Glu Asn Pro Gly Pro
            500                 505                 510
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Met Ala His Ala Gly Arg Thr Gly Tyr Asp Asn Arg Glu Ile Val Met
515 520 525

Lys Tyr Ile His Tyr Lys Leu Ser Gln Arg Gly Tyr Glu Trp Asp Ala
530 535 540

Gly Asp Val Gly Ala Ala Pro Pro Gly Ala Ala Pro Ala Pro Gly Ile
545 550 555 560

Phe Ser Ser Gln Pro Gly His Thr Pro His Pro Ala Ala Ser Arg Asp
565 570 575

Pro Val Ala Arg Thr Ser Pro Leu Gln Thr Pro Ala Ala Pro Gly Ala
580 585 590

Ala Ala Gly Pro Ala Leu Ser Pro Val Pro Pro Val Val His Leu Thr
595 600 605

Leu Arg Gln Ala Gly Asp Asp Phe Ser Arg Arg Tyr Arg Arg Asp Phe
610 615 620

Ala Glu Met Ser Ser Gln Leu His Leu Thr Pro Phe Thr Ala Arg Gly
625 630 635 640

Arg Phe Ala Thr Val Val Glu Glu Leu Phe Arg Asp Gly Val Asn Trp
645 650 655

Gly Arg Ile Val Ala Phe Phe Glu Phe Gly Gly Val Met Cys Val Glu
660 665 670

Ser Val Asn Arg Glu Met Ser Pro Leu Val Asp Asn Ile Ala Leu Trp
675 680 685

Met Thr Glu Tyr Leu Asn Arg His Leu His Thr Trp Ile Gln Asp Asn
690 695 700

Gly Gly Trp Asp Ala Phe Val Glu Leu Tyr Gly Pro Ser Met Arg Pro
705 710 715 720

Leu Phe Asp Phe Ser Trp Leu Ser Leu Lys Thr Leu Leu Ser Leu Ala
725 730 735

Leu Val Gly Ala Cys Ile Thr Leu Gly Ala Tyr Leu Gly His Lys
740 745 750

<210> SEQ ID NO 58
<211> LENGTH: 490
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: GC33BBZ

<400> SEQUENCE: 58

Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1 5 10 15

Gly Ser Thr Gly Thr Gly Asp Val Val Met Thr Gln Ser Pro Leu Ser
20 25 30

Leu Pro Val Thr Pro Gly Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser
35 40 45

Gln Ser Leu Val His Ser Asn Ala Asn Thr Tyr Leu His Trp Tyr Leu
50 55 60

Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn
65 70 75 80

Arg Phe Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr
85 90 95

Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val
100 105 110

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Tyr Tyr Cys Ser Gln Asn Thr His Val Pro Pro Thr Phe Gly Gln Gly
        115                 120                 125

Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
    130                 135                 140

Gly Gly Gly Gly Ser Gln Val Gln Leu Val Glu Ser Gly Ala Glu Val
145                 150                 155                 160

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
                165                 170                 175

Thr Phe Thr Asp Tyr Glu Met His Trp Val Arg Gln Ala Pro Gly Gln
            180                 185                 190

Gly Leu Glu Trp Met Gly Ala Leu Asp Pro Lys Thr Gly Asp Thr Ala
        195                 200                 205

Tyr Ser Gln Lys Phe Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser
    210                 215                 220

Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr
225                 230                 235                 240

Ala Val Tyr Tyr Cys Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln
                245                 250                 255

Gly Thr Leu Val Thr Val Ser Ser Ala Ala Ala Thr Thr Thr Pro Ala
            260                 265                 270

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser
        275                 280                 285

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr
    290                 295                 300

Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala
305                 310                 315                 320

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
                325                 330                 335

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
            340                 345                 350

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
        355                 360                 365

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg
    370                 375                 380

Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn
385                 390                 395                 400

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
                405                 410                 415

Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro
            420                 425                 430

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
        435                 440                 445

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
    450                 455                 460

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
465                 470                 475                 480

Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490
```

<210> SEQ ID NO 59
<211> LENGTH: 755

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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: GC179BBZ-Bcl-2

<400> SEQUENCE: 59

Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1 5 10 15

Gly Ser Thr Gly Thr Gly Asp Ile Val Met Thr Gln Ser Ala Pro Ser
20 25 30

Val Pro Val Thr Pro Gly Glu Ser Val Ser Ile Ser Cys Lys Ser Ser
35 40 45

Lys Ser Leu Leu His Ser Asn Gly Asn Thr Tyr Leu Asn Trp Phe Leu
50 55 60

Gln Arg Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Trp Met Ser Asn
65 70 75 80

Leu Ala Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr
85 90 95

Ala Phe Thr Leu Arg Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val
100 105 110

Tyr Tyr Cys Met Gln His Ile Glu Tyr Pro Phe Thr Phe Gly Thr Gly
115 120 125

Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
130 135 140

Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Thr Gly Gly Gly Leu
145 150 155 160

Val Gln Pro Glu Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe
165 170 175

Ser Phe Asn Ile Asn Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys
180 185 190

Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Glu Ser Asn Asn Tyr Ala
195 200 205

Thr Tyr Tyr Gly Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp
210 215 220

Asp Ser Gln Asn Met Leu Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu
225 230 235 240

Asp Thr Ala Ile Tyr Tyr Cys Val Arg Glu Val Thr Thr Ser Phe Ala
245 250 255

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala Ala Ala Ala Thr
260 265 270

Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser
275 280 285

Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly
290 295 300

Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp
305 310 315 320

Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile
325 330 335

Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys
340 345 350

Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys
355 360 365

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Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val
    370                 375                 380

Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn
385                 390                 395                 400

Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val
                405                 410                 415

Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg
            420                 425                 430

Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys
        435                 440                 445

Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg
    450                 455                 460

Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys
465                 470                 475                 480

Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg Gly Ser
                485                 490                 495

Gly Ala Thr Asn Phe Ser Leu Leu Lys Gln Ala Gly Asp Val Glu Glu
            500                 505                 510

Asn Pro Gly Pro Met Ala His Ala Gly Arg Thr Gly Tyr Asp Asn Arg
        515                 520                 525

Glu Ile Val Met Lys Tyr Ile His Tyr Lys Leu Ser Gln Arg Gly Tyr
    530                 535                 540

Glu Trp Asp Ala Gly Asp Val Gly Ala Ala Pro Pro Gly Ala Ala Pro
545                 550                 555                 560

Ala Pro Gly Ile Phe Ser Ser Gln Pro Gly His Thr Pro His Pro Ala
                565                 570                 575

Ala Ser Arg Asp Pro Val Ala Arg Thr Ser Pro Leu Gln Thr Pro Ala
            580                 585                 590

Ala Pro Gly Ala Ala Ala Gly Pro Ala Leu Ser Pro Val Pro Pro Val
        595                 600                 605

Val His Leu Thr Leu Arg Gln Ala Gly Asp Asp Phe Ser Arg Arg Tyr
    610                 615                 620

Arg Arg Asp Phe Ala Glu Met Ser Ser Gln Leu His Leu Thr Pro Phe
625                 630                 635                 640

Thr Ala Arg Gly Arg Phe Ala Thr Val Val Glu Glu Leu Phe Arg Asp
                645                 650                 655

Gly Val Asn Trp Gly Arg Ile Val Ala Phe Phe Glu Phe Gly Gly Val
            660                 665                 670

Met Cys Val Glu Ser Val Asn Arg Glu Met Ser Pro Leu Val Asp Asn
        675                 680                 685

Ile Ala Leu Trp Met Thr Glu Tyr Leu Asn Arg His Leu His Thr Trp
    690                 695                 700

Ile Gln Asp Asn Gly Gly Trp Asp Ala Phe Val Glu Leu Tyr Gly Pro
705                 710                 715                 720

Ser Met Arg Pro Leu Phe Asp Phe Ser Trp Leu Ser Leu Lys Thr Leu
                725                 730                 735

Leu Ser Leu Ala Leu Val Gly Ala Cys Ile Thr Leu Gly Ala Tyr Leu
            740                 745                 750

Gly His Lys
        755
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<210> SEQ ID NO 60
<211> LENGTH: 494
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: GC179BBZ

<400> SEQUENCE: 60

Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1 5 10 15

Gly Ser Thr Gly Thr Gly Asp Ile Val Met Thr Gln Ser Ala Pro Ser
20 25 30

Val Pro Val Thr Pro Gly Glu Ser Val Ser Ile Ser Cys Lys Ser Ser
35 40 45

Lys Ser Leu Leu His Ser Asn Gly Asn Thr Tyr Leu Asn Trp Phe Leu
50 55 60

Gln Arg Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Trp Met Ser Asn
65 70 75 80

Leu Ala Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr
85 90 95

Ala Phe Thr Leu Arg Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val
100 105 110

Tyr Tyr Cys Met Gln His Ile Glu Tyr Pro Phe Thr Phe Gly Thr Gly
115 120 125

Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
130 135 140

Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Thr Gly Gly Gly Leu
145 150 155 160

Val Gln Pro Glu Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe
165 170 175

Ser Phe Asn Ile Asn Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys
180 185 190

Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Glu Ser Asn Asn Tyr Ala
195 200 205

Thr Tyr Tyr Gly Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp
210 215 220

Asp Ser Gln Asn Met Leu Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu
225 230 235 240

Asp Thr Ala Ile Tyr Tyr Cys Val Arg Glu Val Thr Thr Ser Phe Ala
245 250 255

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala Ala Ala Ala Thr
260 265 270

Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser
275 280 285

Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly
290 295 300

Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp
305 310 315 320

Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile
325 330 335

Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys
340 345 350

Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys

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        355                 360                 365

Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val
    370                 375                 380

Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn
385                 390                 395                 400

Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val
                405                 410                 415

Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg
            420                 425                 430

Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys
        435                 440                 445

Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg
    450                 455                 460

Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys
465                 470                 475                 480

Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490


<210> SEQ ID NO 61
<211> LENGTH: 726
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: M3C11BBZ-Bcl-2

<400> SEQUENCE: 61

Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1               5                   10                  15

Gly Ser Thr Gly Thr Gly Asp Val Val Met Thr Gln Thr Pro Leu Thr
            20                  25                  30

Leu Ser Val Thr Ile Gly Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser
        35                  40                  45

Gln Ser Leu Leu Asp Ser Asp Gly Lys Thr Tyr Leu Asn Trp Leu Leu
    50                  55                  60

Gln Arg Pro Gly Gln Ser Pro Lys Arg Leu Ile Tyr Leu Val Ser Lys
65                  70                  75                  80

Leu Asp Ser Gly Ala Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr
                85                  90                  95

Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Ile
            100                 105                 110

Tyr Tyr Cys Trp Gln Gly Thr His Phe Pro Leu Thr Phe Gly Ala Gly
        115                 120                 125

Thr Lys Leu Glu Leu Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
    130                 135                 140

Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
145                 150                 155                 160

Val Lys Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe
                165                 170                 175

Thr Phe Ser Arg Tyr Ala Met Ser Trp Val Arg Gln Ile Pro Glu Lys
            180                 185                 190

Ile Leu Glu Trp Val Ala Ala Ile Asp Ser Ser Gly Gly Asp Thr Tyr
        195                 200                 205

Tyr Leu Asp Thr Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asn Ala
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    210                 215                 220

Asn Asn Thr Leu His Leu Gln Met Arg Ser Leu Arg Ser Glu Asp Thr
225                 230                 235                 240

Ala Leu Tyr Tyr Cys Val Arg Gln Gly Gly Ala Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Leu Val Thr Val Ser Ala Ala Thr Thr Thr Pro Ala Pro Arg Pro
            260                 265                 270

Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
        275                 280                 285

Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu
    290                 295                 300

Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
305                 310                 315                 320

Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly
                325                 330                 335

Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
            340                 345                 350

Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu
        355                 360                 365

Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp
    370                 375                 380

Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
385                 390                 395                 400

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
                405                 410                 415

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
            420                 425                 430

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
        435                 440                 445

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
    450                 455                 460

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
465                 470                 475                 480

Met Gln Ala Leu Pro Pro Arg Met Ala His Ala Gly Arg Thr Gly Tyr
                485                 490                 495

Asp Asn Arg Glu Ile Val Met Lys Tyr Ile His Tyr Lys Leu Ser Gln
            500                 505                 510

Arg Gly Tyr Glu Trp Asp Ala Gly Asp Val Gly Ala Ala Pro Pro Gly
        515                 520                 525

Ala Ala Pro Ala Pro Gly Ile Phe Ser Ser Gln Pro Gly His Thr Pro
    530                 535                 540

His Pro Ala Ala Ser Arg Asp Pro Val Ala Arg Thr Ser Pro Leu Gln
545                 550                 555                 560

Thr Pro Ala Ala Pro Gly Ala Ala Ala Gly Pro Ala Leu Ser Pro Val
                565                 570                 575

Pro Pro Val Val His Leu Thr Leu Arg Gln Ala Gly Asp Asp Phe Ser
            580                 585                 590

Arg Arg Tyr Arg Arg Asp Phe Ala Glu Met Ser Ser Gln Leu His Leu
        595                 600                 605

Thr Pro Phe Thr Ala Arg Gly Arg Phe Ala Thr Val Val Glu Glu Leu
    610                 615                 620
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Phe Arg Asp Gly Val Asn Trp Gly Arg Ile Val Ala Phe Phe Glu Phe
625                 630                 635                 640

Gly Gly Val Met Cys Val Glu Ser Val Asn Arg Glu Met Ser Pro Leu
                645                 650                 655

Val Asp Asn Ile Ala Leu Trp Met Thr Glu Tyr Leu Asn Arg His Leu
            660                 665                 670

His Thr Trp Ile Gln Asp Asn Gly Gly Trp Asp Ala Phe Val Glu Leu
        675                 680                 685

Tyr Gly Pro Ser Met Arg Pro Leu Phe Asp Phe Ser Trp Leu Ser Leu
    690                 695                 700

Lys Thr Leu Leu Ser Leu Ala Leu Val Gly Ala Cys Ile Thr Leu Gly
705                 710                 715                 720

Ala Tyr Leu Gly His Lys
                725


<210> SEQ ID NO 62
<211> LENGTH: 487
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: M3C11BBZ

<400> SEQUENCE: 62

Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1               5                   10                  15

Gly Ser Thr Gly Thr Gly Asp Val Val Met Thr Gln Thr Pro Leu Thr
            20                  25                  30

Leu Ser Val Thr Ile Gly Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser
        35                  40                  45

Gln Ser Leu Leu Asp Ser Asp Gly Lys Thr Tyr Leu Asn Trp Leu Leu
    50                  55                  60

Gln Arg Pro Gly Gln Ser Pro Lys Arg Leu Ile Tyr Leu Val Ser Lys
65                  70                  75                  80

Leu Asp Ser Gly Ala Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr
                85                  90                  95

Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Ile
            100                 105                 110

Tyr Tyr Cys Trp Gln Gly Thr His Phe Pro Leu Thr Phe Gly Ala Gly
        115                 120                 125

Thr Lys Leu Glu Leu Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
    130                 135                 140

Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
145                 150                 155                 160

Val Lys Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe
                165                 170                 175

Thr Phe Ser Arg Tyr Ala Met Ser Trp Val Arg Gln Ile Pro Glu Lys
            180                 185                 190

Ile Leu Glu Trp Val Ala Ala Ile Asp Ser Ser Gly Gly Asp Thr Tyr
        195                 200                 205

Tyr Leu Asp Thr Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asn Ala
    210                 215                 220

Asn Asn Thr Leu His Leu Gln Met Arg Ser Leu Arg Ser Glu Asp Thr
225                 230                 235                 240
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Ala Leu Tyr Tyr Cys Val Arg Gln Gly Gly Ala Tyr Trp Gly Gln Gly
               245                 250                 255

Thr Leu Val Thr Val Ser Ala Ala Thr Thr Thr Pro Ala Pro Arg Pro
            260                 265                 270

Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
        275                 280                 285

Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu
    290                 295                 300

Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
305                 310                 315                 320

Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly
                325                 330                 335

Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
            340                 345                 350

Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu
        355                 360                 365

Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp
    370                 375                 380

Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
385                 390                 395                 400

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
                405                 410                 415

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
            420                 425                 430

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
        435                 440                 445

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
    450                 455                 460

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
465                 470                 475                 480

Met Gln Ala Leu Pro Pro Arg
                485
```

1. An immune effector cell, comprising and/or expressing a chimeric antigen receptor (CAR), and a Bcl-2 protein or a functionally active fragment thereof.

2. The immune effector cell according to claim **1**, wherein the CAR comprises an antigen binding domain, and the antigen binding domain comprises an antibody specifically binding to CD20 or an antigen binding fragment thereof.

3. The immune effector cell according to claim **2**, wherein the antibody or the antigen binding fragment thereof comprises a HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3,

wherein the HCDR1 comprises an amino acid sequence as set forth in SEQ ID NO: 3,

wherein the HCDR2 comprises an amino acid sequence as set forth in SEQ ID NO: 2,

wherein the HCDR3 comprises an amino acid sequence as set forth in SEQ ID NO: 1,

wherein the LCDR1 comprises an amino acid sequence as set forth in SEQ ID NO: 6,

wherein the LCDR2 comprises an amino acid sequence as set forth in SEQ ID NO: 5, and

wherein the LCDR3 comprises an amino acid sequence as set forth in SEQ ID NO: 4.

4-8. (canceled)

9. The immune effector cell according to claim **2**, wherein the antibody or the antigen binding fragment thereof comprises a VH and a VL,

wherein the VH comprises an amino acid sequence as set forth in SEQ ID NO: 7, and

wherein the VL comprises an amino acid sequence as set forth in SEQ ID NO: 8.

10-11. (canceled)

12. The immune effector cell according to claim **1**, wherein the CAR comprises an antigen binding domain, and the antigen binding domain comprises an antibody specifically binding to CLDN18.2 or an antigen binding fragment thereof.

13. The immune effector cell according to claim **12**, wherein the antibody or the antigen binding fragment thereof comprises a HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3,

wherein the HCDR1 comprises an amino acid sequence as set forth in SEQ ID NO: 13,

wherein the HCDR2 comprises an amino acid sequence as set forth in SEQ ID NO: 12,

wherein the HCDR3 comprises an amino acid sequence as set forth in SEQ ID NO: 11,

wherein the LCDR1 comprises an amino acid sequence as set forth in SEQ ID NO: 16,

wherein the LCDR2 comprises an amino acid sequence as set forth in SEQ ID NO: 15, and

wherein the LCDR3 comprises an amino acid sequence as set forth in SEQ ID NO: 14.

14-18. (canceled)

19. The immune effector cell according to claim **12**, wherein the antibody or the antigen binding fragment thereof comprises a VH and a VL,

wherein the VH comprises an amino acid sequence as set forth in SEQ ID NO: 17, and

wherein the VL comprises an amino acid sequence as set forth in SEQ ID NO: 18.

20-21. (canceled)

22. The immune effector cell according to claim **1**, wherein the CAR comprises an antigen binding domain, and the antigen binding domain comprises an antibody or an antigen binding fragment thereof specifically binding to GPC-3.

23. The immune effector cell according to claim **22**, wherein the antibody or the antigen binding fragment thereof comprises a HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3,

wherein the HCDR1 comprises an amino acid sequence as set forth in SEQ ID NO: 22, SEQ ID NO: 31, and SEQ ID NO: 40,

wherein the HCDR2 comprises an amino acid sequence as set forth in SEQ ID NO: 21, SEQ ID NO: 30, and SEQ ID NO: 39,

wherein the HCDR3 comprises an amino acid sequence as set forth in SEQ ID NO: 20 SEQ ID NO: 29, and SEQ ID NO: 38,

wherein the LCDR1 comprises an amino acid sequence as set forth in SEQ ID NO: 25, SEQ ID NO: 34, and SEQ ID NO:43,

wherein the LCDR2 comprises an amino acid sequence as set forth in SEQ ID NO: 24, SEQ ID NO: 33, and SEQ ID NO: 42, and

wherein the LCDR3 comprises an amino acid sequence as set forth in SEQ ID NO: 23, SEQ ID NO: 32 and SEQ ID NO: 41.

24-28. (canceled)

29. The immune effector cell according to claim **22**, wherein the antibody or the antigen binding fragment thereof comprises a VH and a VL,

wherein the VH comprises an amino acid sequence as set forth in any one of SEQ ID NO: 26, SEQ ID NO: 35, and SEQ ID NO: 44, and

wherein the VL comprises an amino acid sequence as set forth in any one of SEQ ID NO: 27, SEQ ID NO: 36, and SEQ ID NO: 45.

30-31. (canceled)

32. The immune effector cell according to claim **2**, wherein the antibody comprises a single-chain antibody.

33. The immune effector cell according to claim **1**, wherein the CAR comprises a transmembrane domain, and the transmembrane domain comprises a transmembrane domain derived from a protein selected from the group consisting of: CD28, CD3e, CD45, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137, and CD154.

34. (canceled)

35. The immune effector cell according to claim **1**, wherein the CAR comprises a co-stimulatory domain, and the co-stimulatory domain comprises one or more co-stimulatory domains of a protein selected from the group consisting of: co-stimulatory signaling regions in CD28, 4-1BB, CD40L, TIM1, CD226, DR3, SLAM, ICOS, OX40, NKG2D, 2B4, CD244, FcεRIγ, BTLA, CD27, CD30, GITR, HVEM, DAP10, CD2, NKG2C, LIGHT, and DAP12.

36. (canceled)

37. The immune effector cell according to claim **1**, wherein the CAR comprises an intracellular signaling domain, and the intracellular signaling domain comprises an intracellular signaling domain derived from CD3ζ.

38. (canceled)

39. The immune effector cell according to claim **1**, wherein the CAR comprises a hinge region, and the hinge region is located between the antigen binding domain and the transmembrane domain.

40-41. (canceled)

42. The immune effector cell according to claim **1**, wherein the CAR comprises an amino acid sequence as set forth in any one of SEQ ID NO: 53, SEQ ID NO: 55, SEQ ID NO: 57, SEQ ID NO: 59, and SEQ ID NO: 61.

43. The immune effector cell according to claim **1**, wherein the Bcl-2 protein or the functionally active fragment thereof is an exogenous Bcl-2 protein or a functionally active fragment thereof.

44. The immune effector cell according to claim **1**, wherein the immune effector cell comprises T cells.

45. The immune effector cell according to claim **1**, wherein the Bcl-2 protein or the functionally active fragment thereof comprises an amino acid sequence as set forth in SEQ ID NO: 52.

46. A nucleic acid molecule encoding the CAR and the Bcl-2 protein or the functionally active fragment thereof of claim **1**.

47. The nucleic acid molecule according to claim **46**, comprising a sequence encoding a self-cleaving peptide located between a sequence encoding the CAR and a sequence encoding the Bcl-2 protein.

48. The nucleic acid molecule according to claim **47**, wherein the self-cleaving peptide comprises a 2A peptide.

49-54. (canceled)

55. A composition, comprising the immune effector cell according to claim **1**.

56. A method for treating diseases and/or disorders, comprising:

administering to a subject in need thereof the immune effector cell according to claim **1**,

wherein the diseases and/or disorders comprise tumors.

57-66. (canceled)

* * * * *