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(54) BISPECIFIC CHIMERIC ANTIGEN RECEPOTRS TARGETING CD20 AND BCMA

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ABSTRACT

The present disclosure provides bispecific chimeric antigen receptors targeting CD20 and BCMA. The CAR may comprise an scFv targeting CD20 and an scFv targeting BCMA, a hinge region, a transmembrane domain, a co-stimulatory region, and a cytoplasmic signaling domain. The chimeric antigen receptors can be used to treat autoimmune disorders or cancer.

Specification includes a Sequence Listing.

IgG4 12aa

TN-OF-B20-1 (TOB1)	SP	OF(VL-VH)	linker	B20(VH-VL)	hinge	CD28TM	4-1BB	CD3z
TN-OF-B20-2 (TOB2)	SP	OF(VL-VH)	linker	B20(VL-VH)	hinge	CD28TM	4-1BB	CD3z
TN-OF-B20-3 (TOB3)	SP	OF(VH-VL)	linker	B20(VL-VH)	hinge	CD28TM	4-1BB	CD3z
TN-OF-B20-4 (TOB4)	SP	OF(VH-VL)	linker	B20(VH-VL)	hinge	CD28TM	4-1BB	CD3z

CD8a 55aa

TN-OF-B20-L1 (TOBL1)	SP	OF(VL-VH)	linker	B20(VL-VH)	hinge	CD8TM	4-1BB	CD3z
TN-OF-B20-L2 (TOBL2)	SP	OF(VH-VL)	linker	B20(VL-VH)	hinge	CD8TM	4-1BB	CD3z
TN-OF-B20-L3 (TOBL3)	SP	OF(VH-VL)	linker	B20(VH-VL)	hinge	CD8TM	4-1BB	CD3z
TN-OF-B20-L4 (TOBL4)	SP	OF(VL-VH)	linker	B20(VH-VL)	hinge	CD8TM	4-1BB	CD3z
C-CAR088	SP			B20(VL-VH)	hinge	CD8TM	4-1BB	CD3z

IgG4 229aa

C-CAR066	SP	OF(VH-VL)		hinge	CD8TM	4-1BB	CD3z
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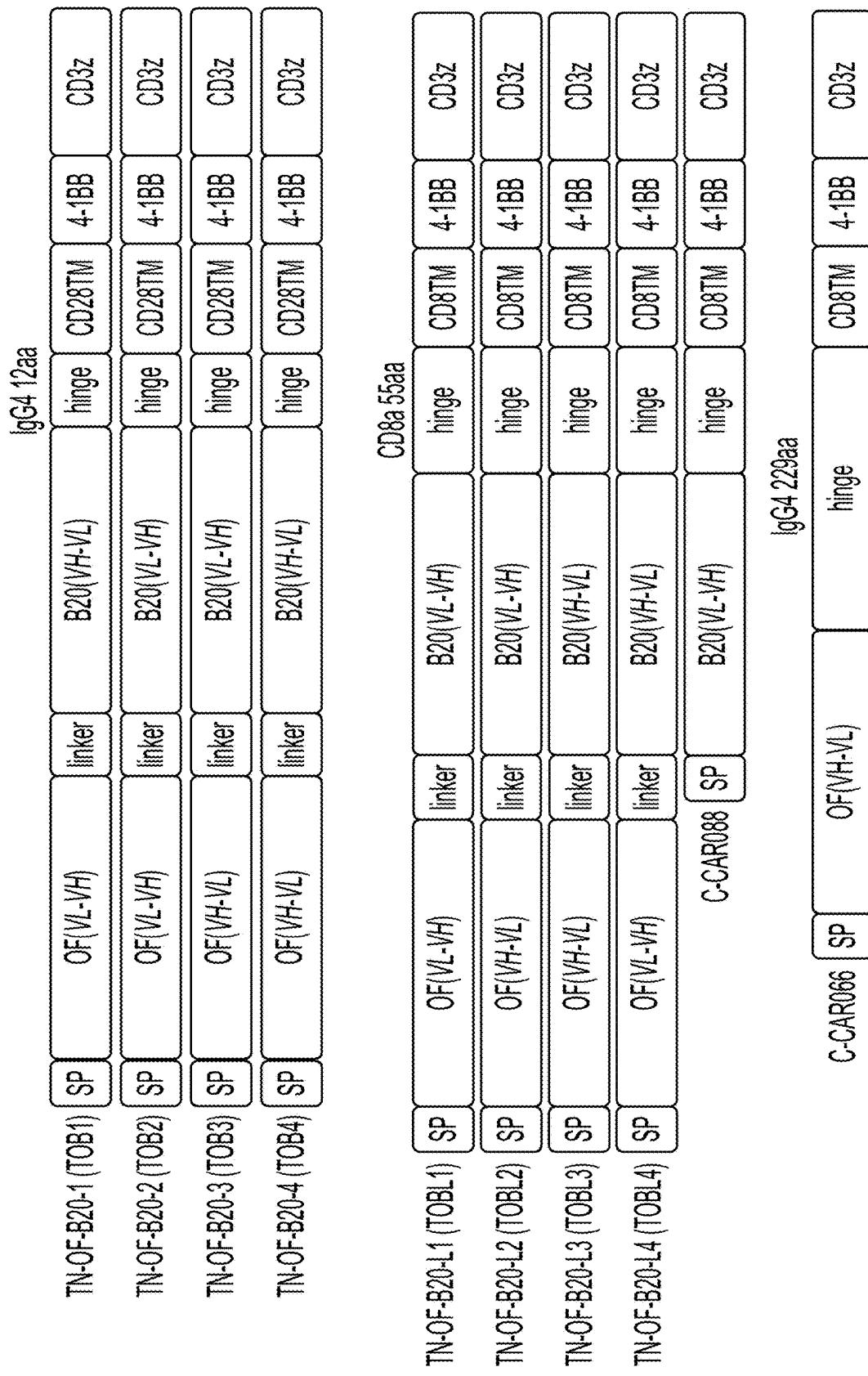


FIG. 1

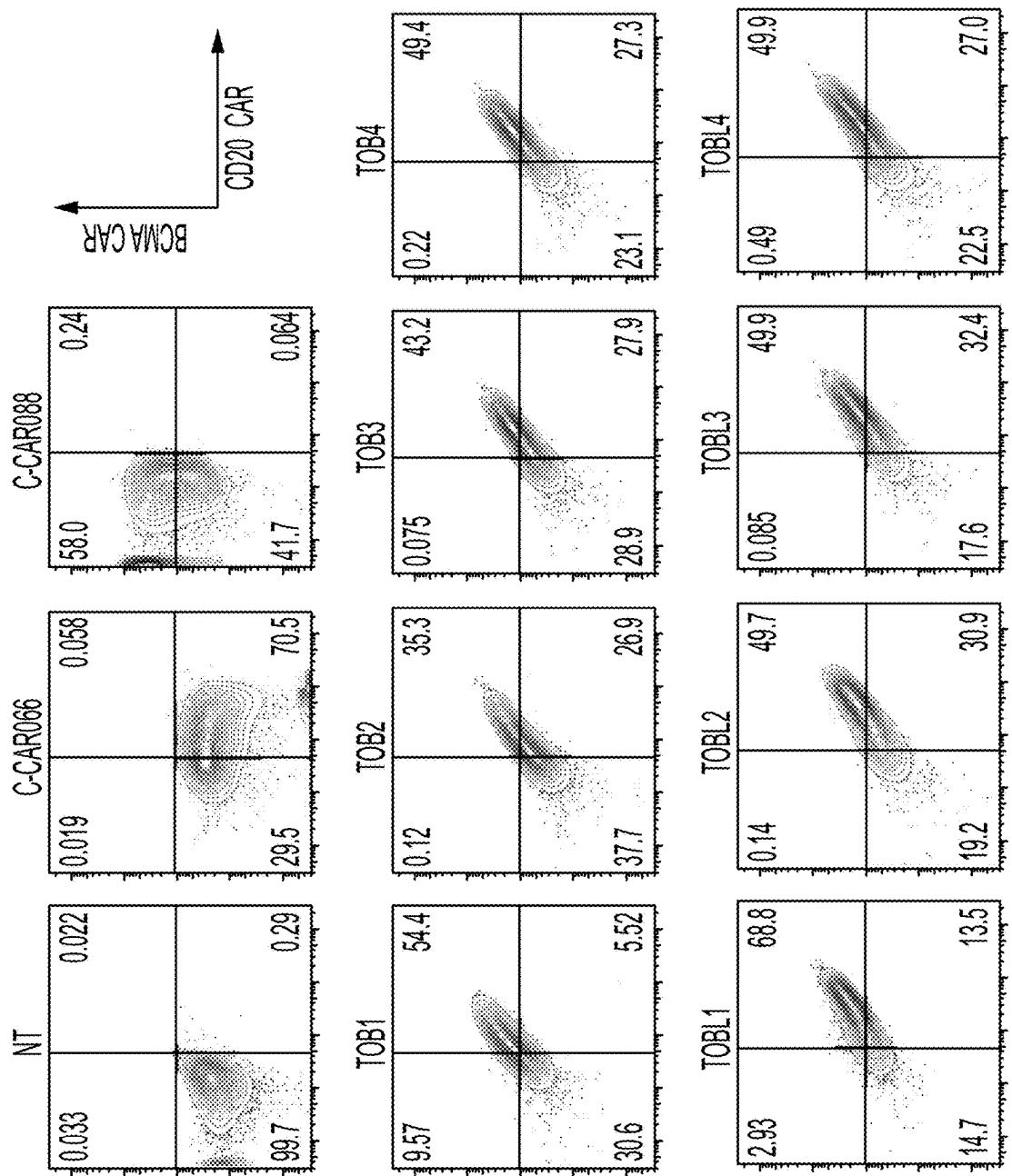


FIG. 2

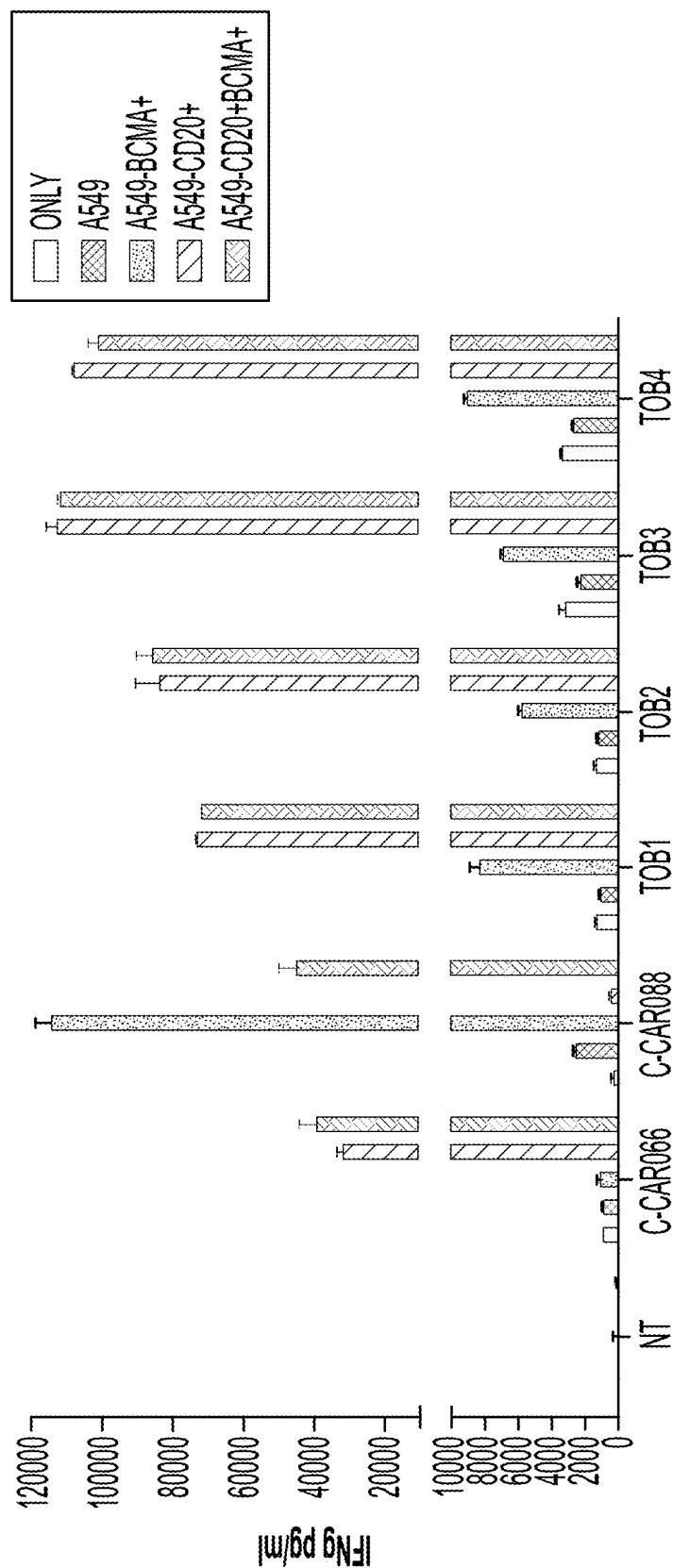


FIG. 3A

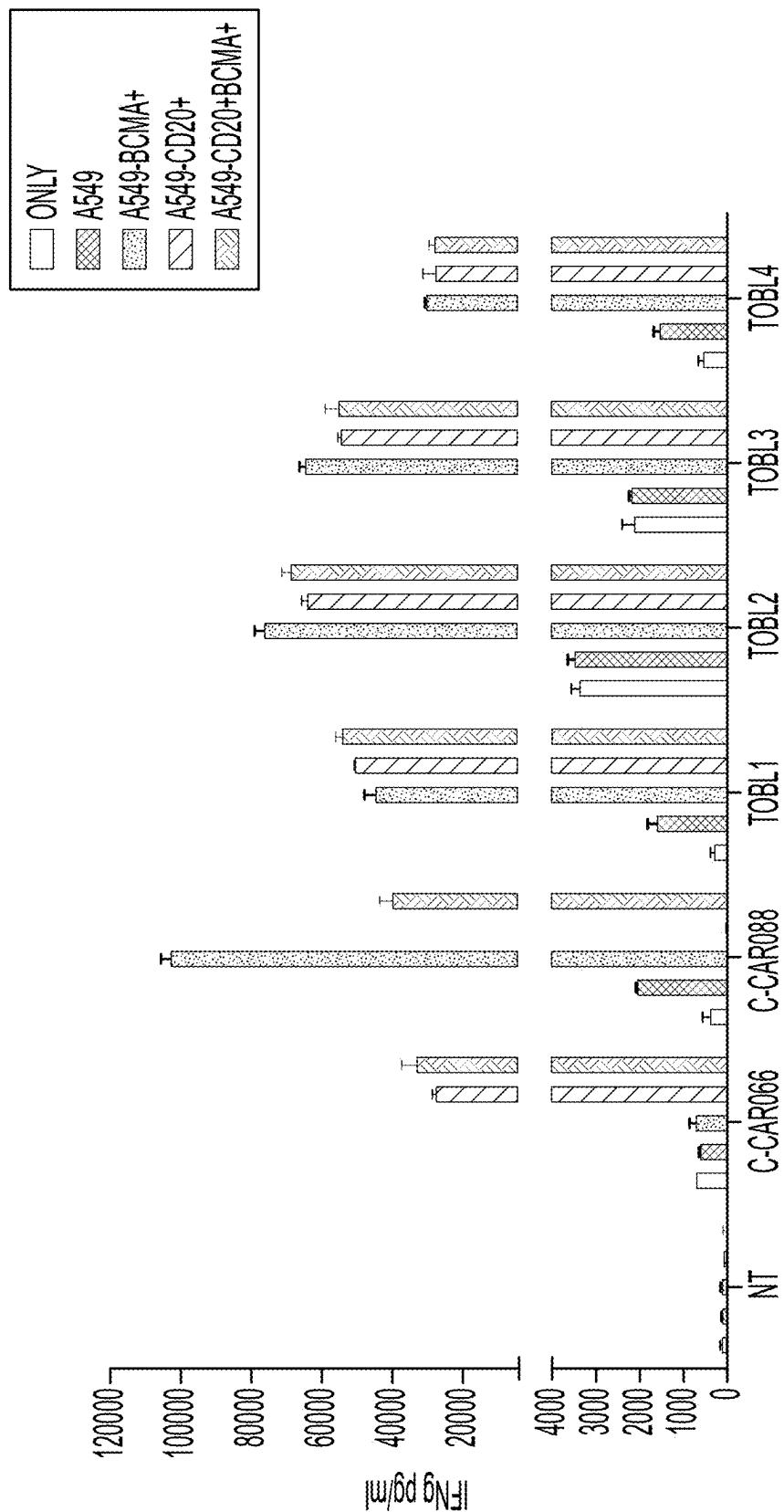


FIG. 3B

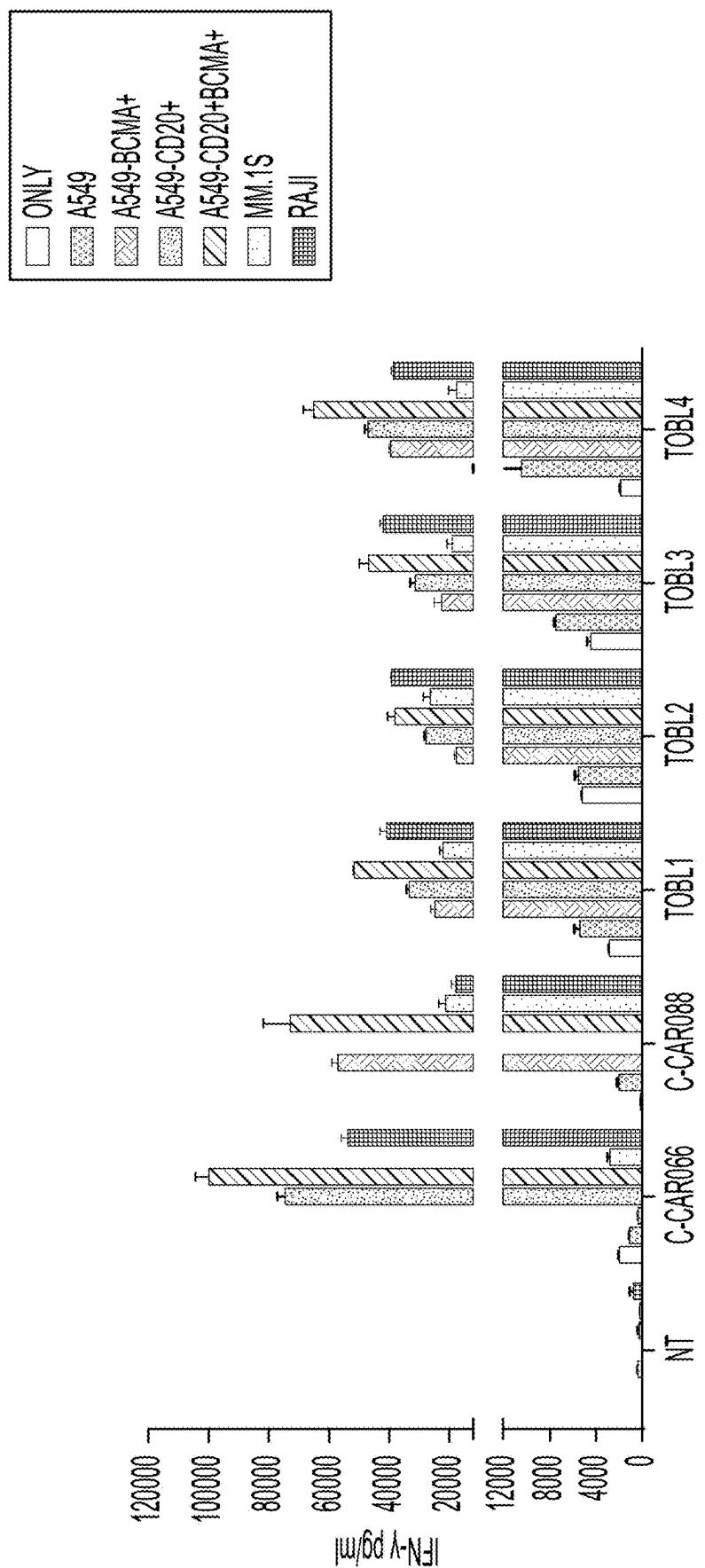


FIG. 3C

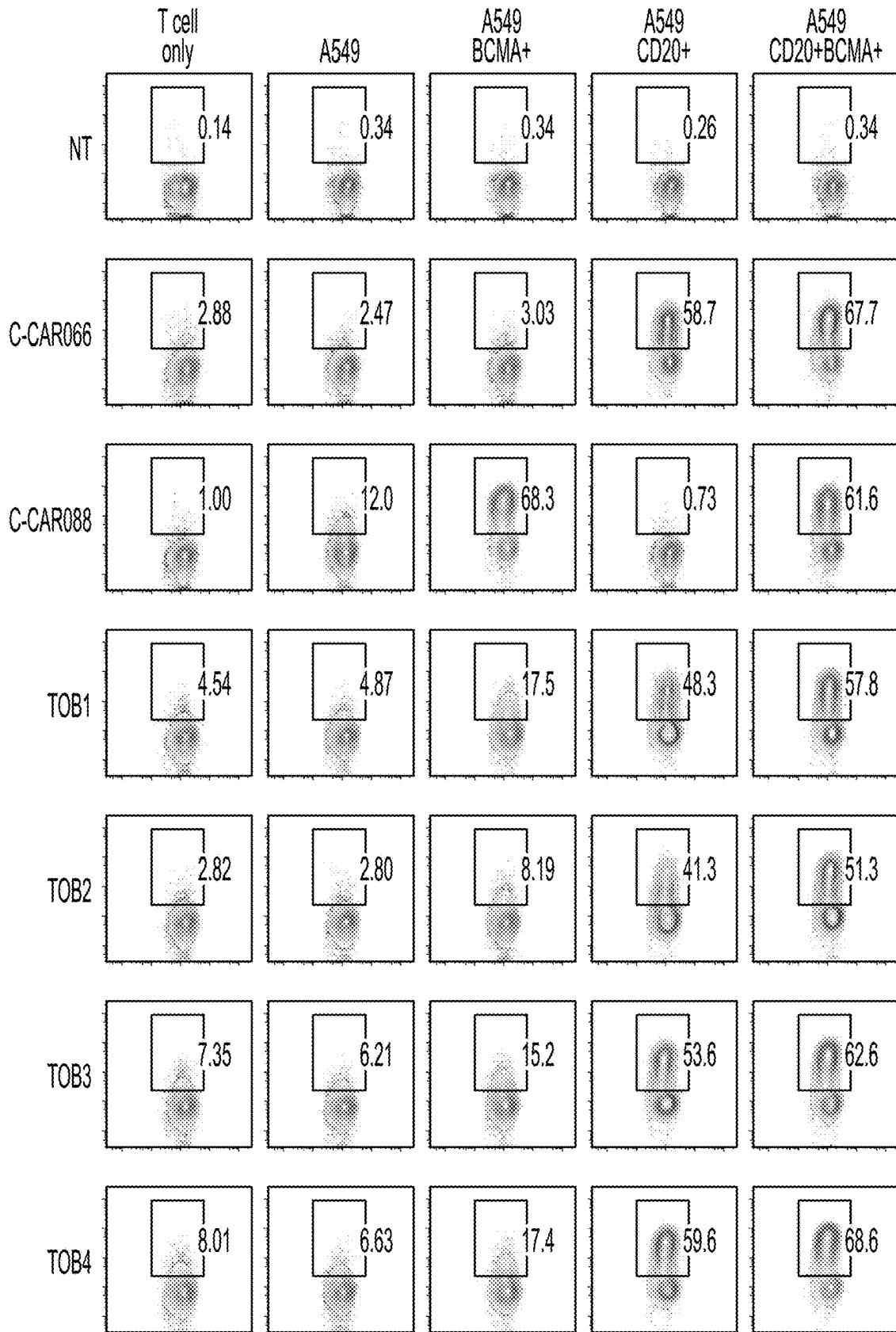


FIG. 4A

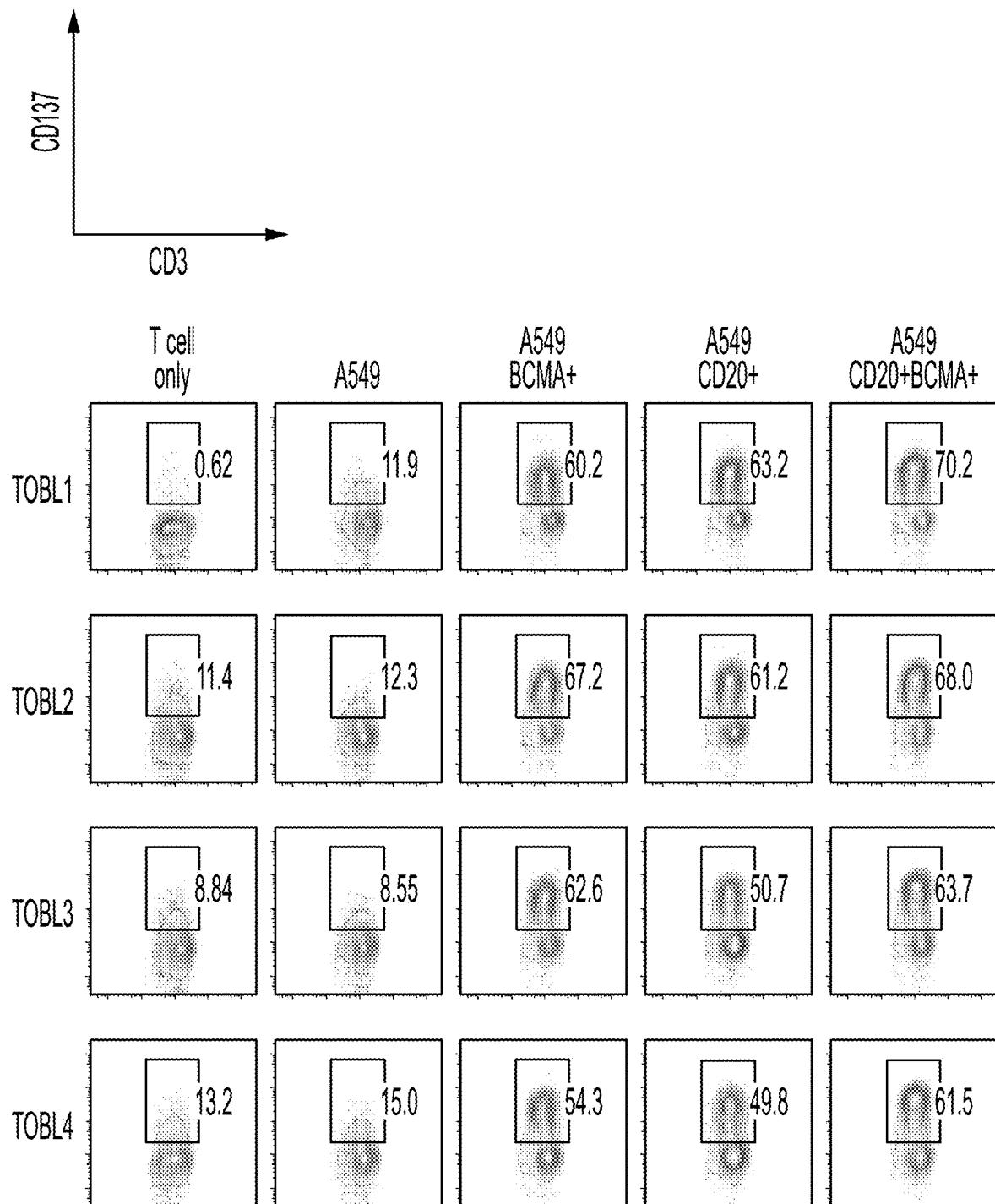


FIG. 4B

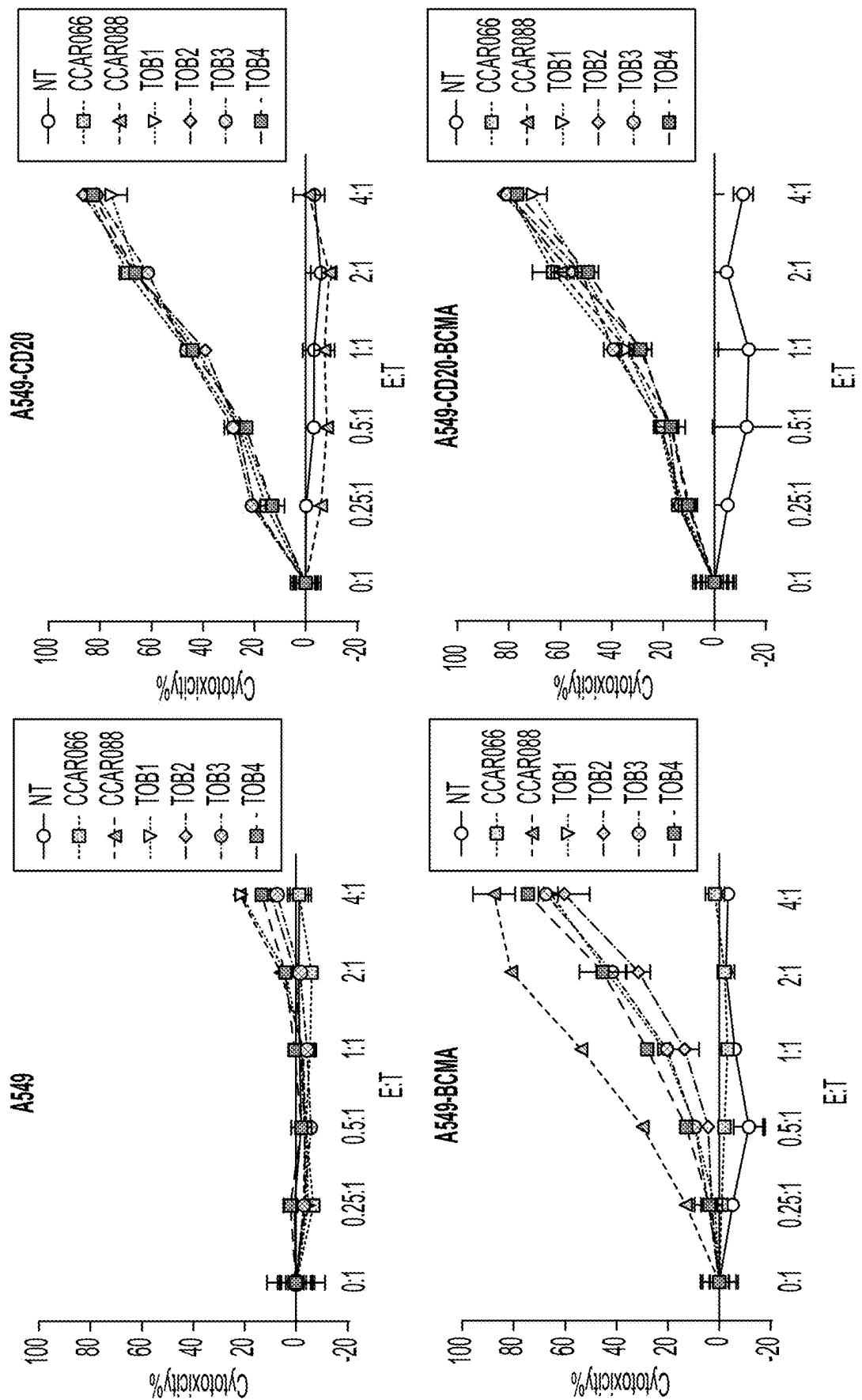
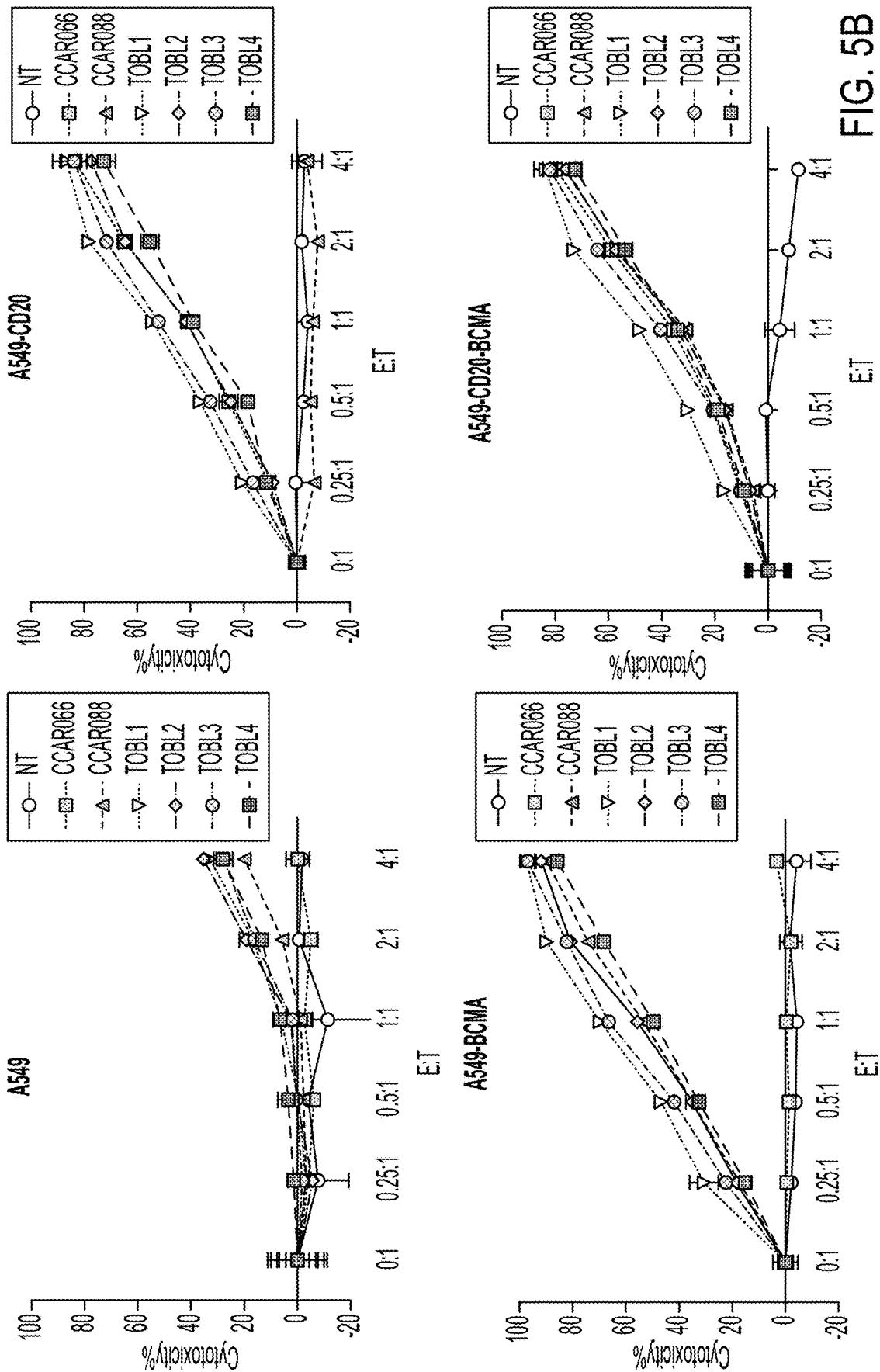


FIG. 5A



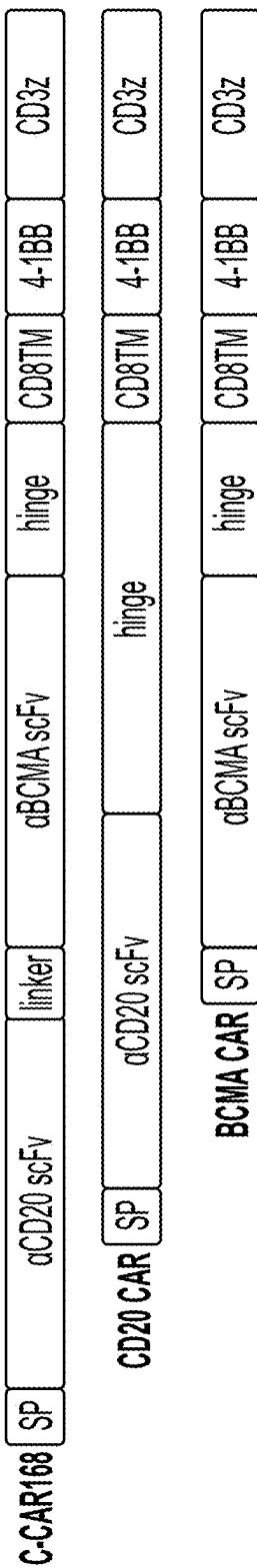


FIG. 6A

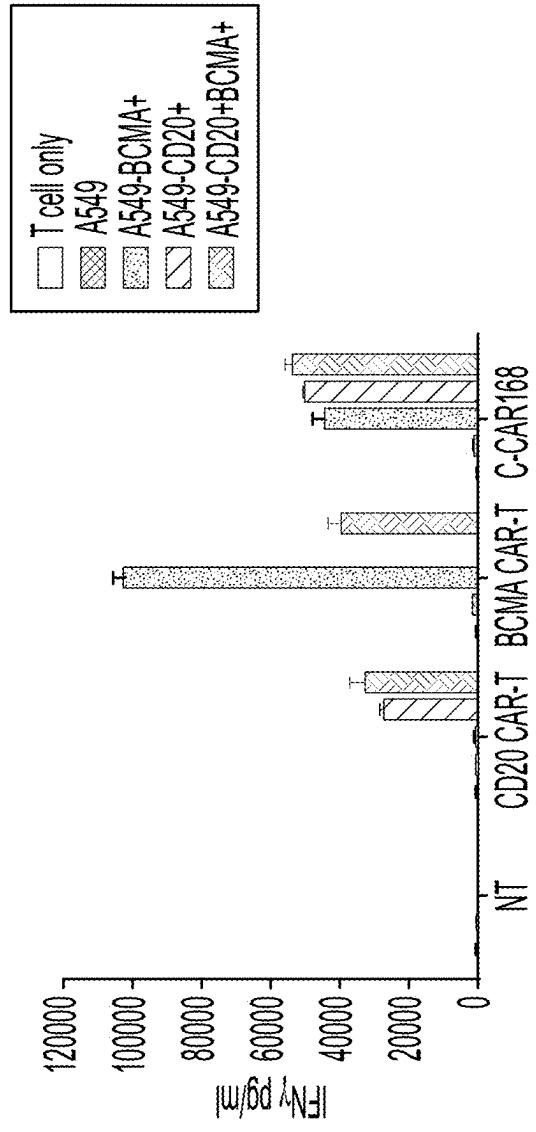


FIG. 6B

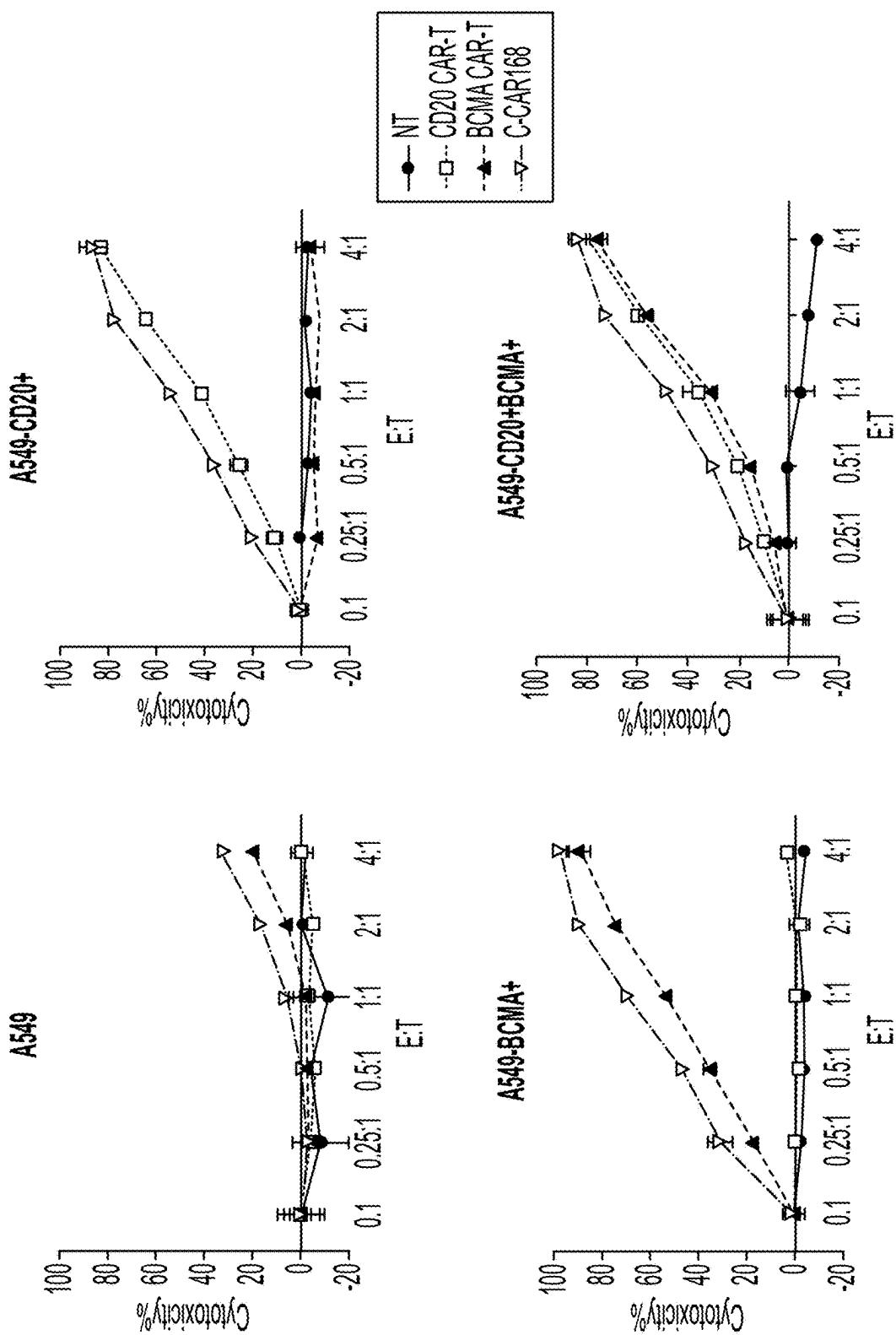


FIG. 6C

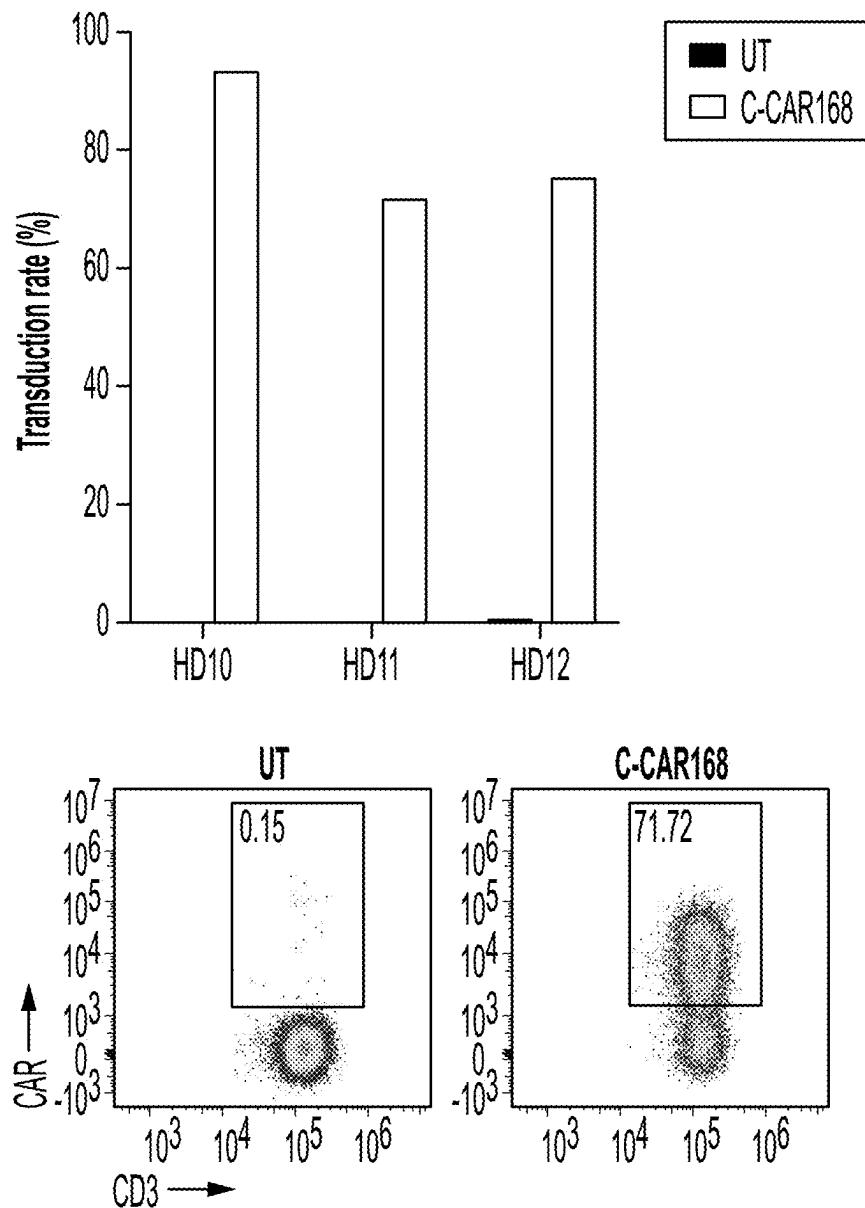


FIG. 7A

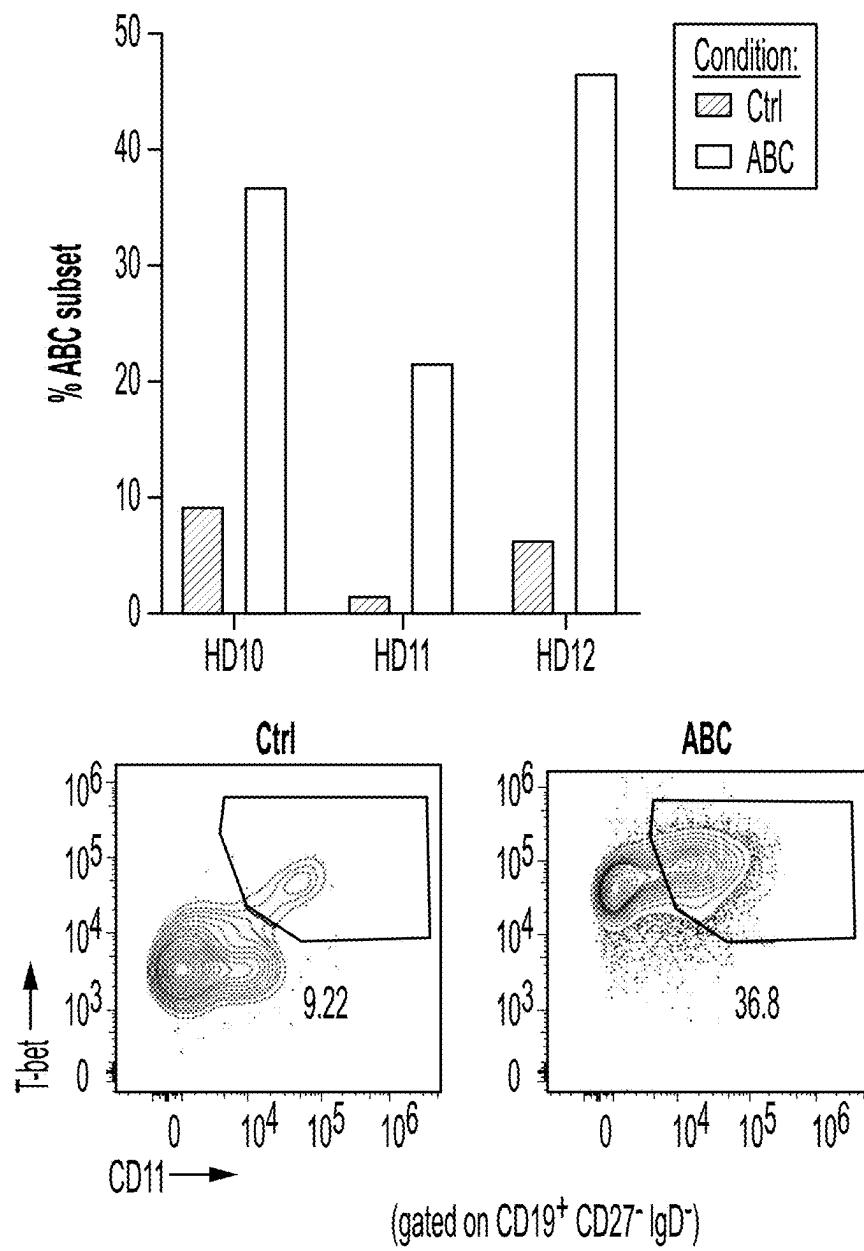


FIG. 7B

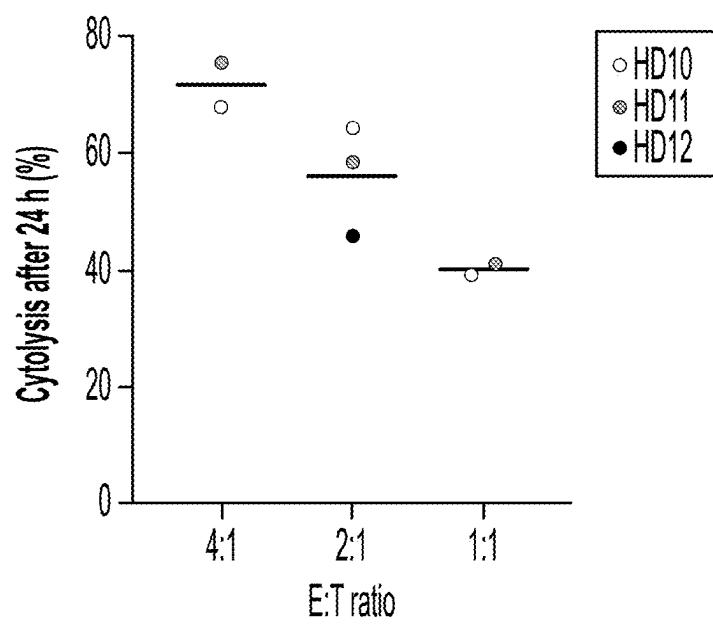


FIG. 7C

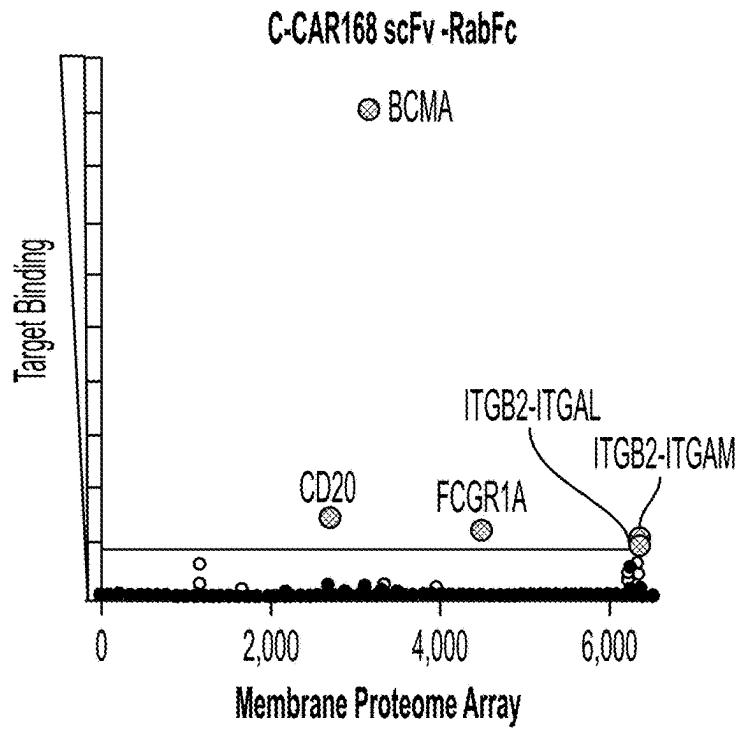


FIG. 8A

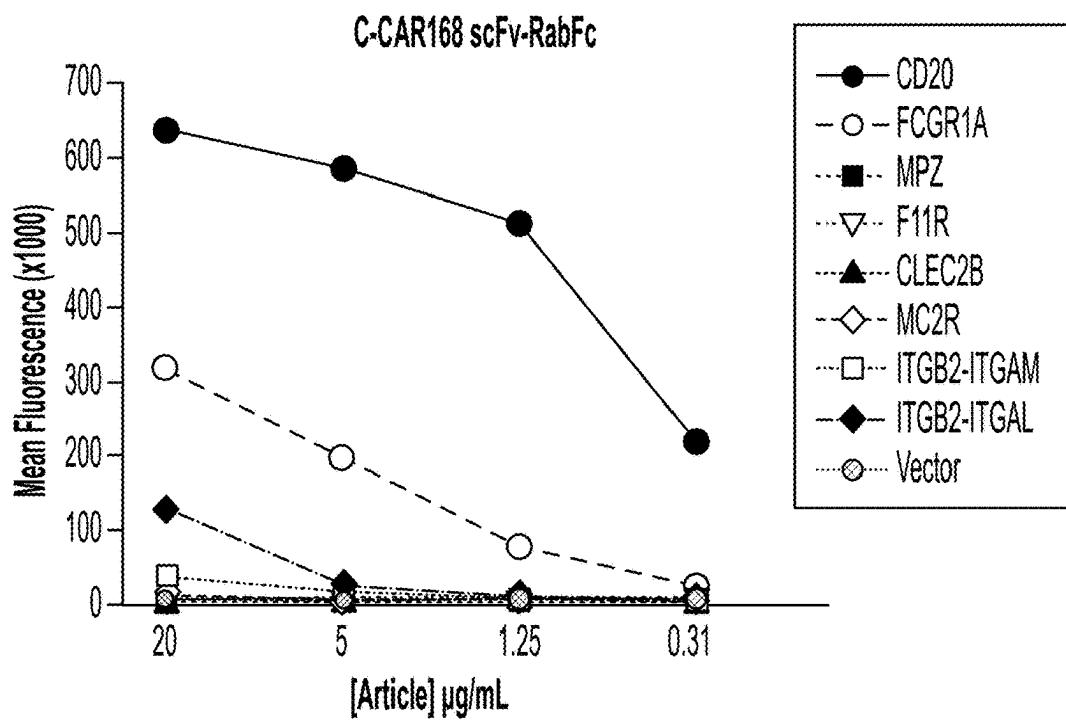


FIG. 8B

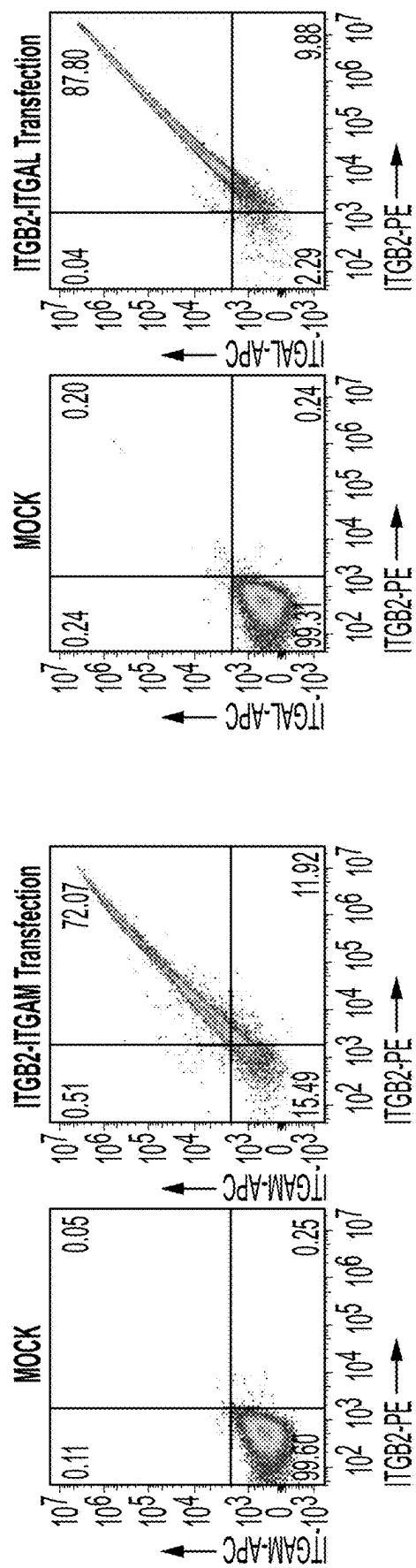


FIG. 8C

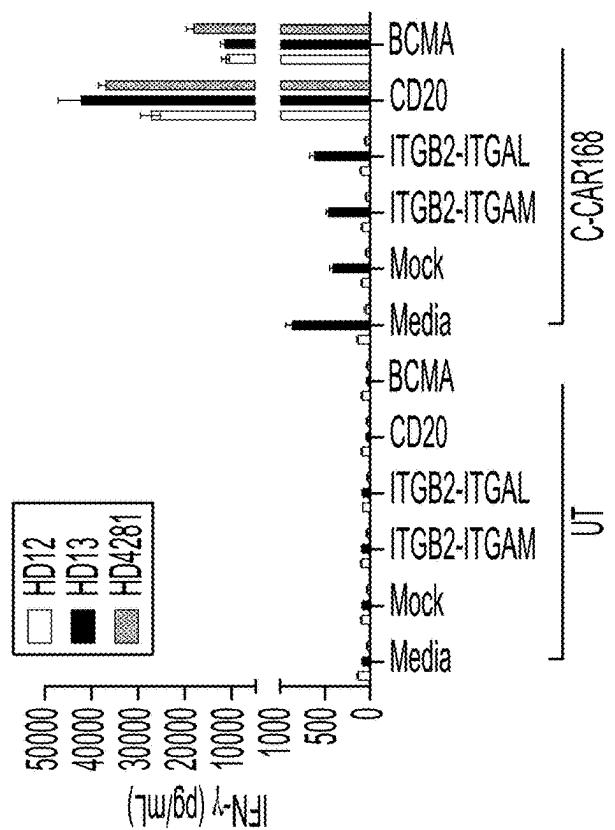
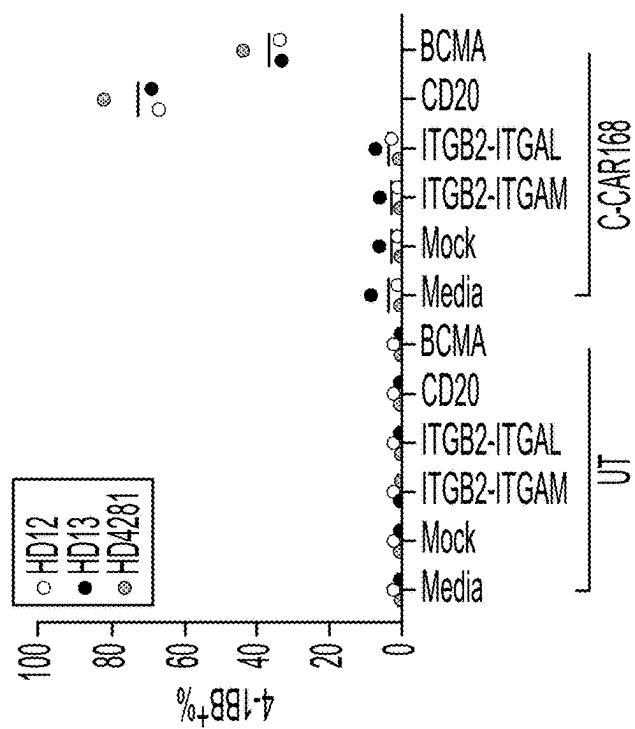


FIG. 8D



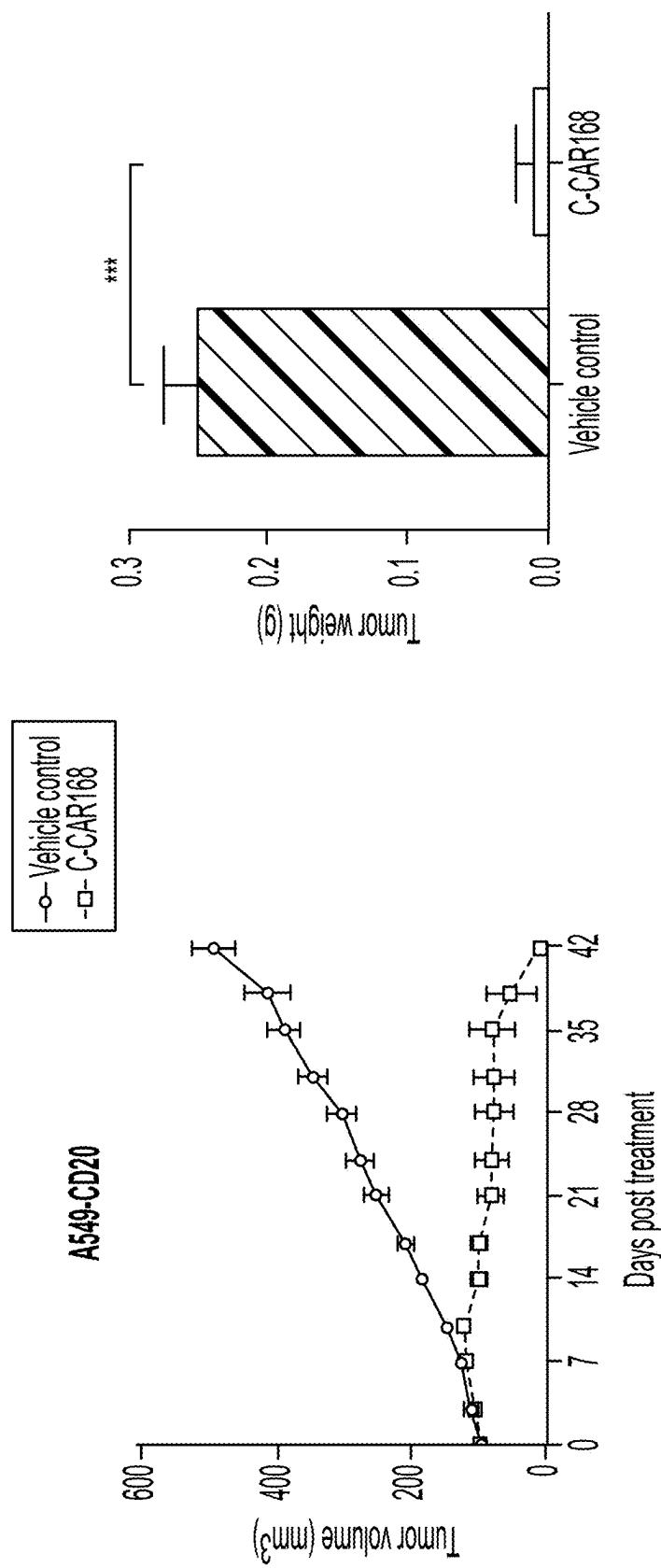


FIG. 9A

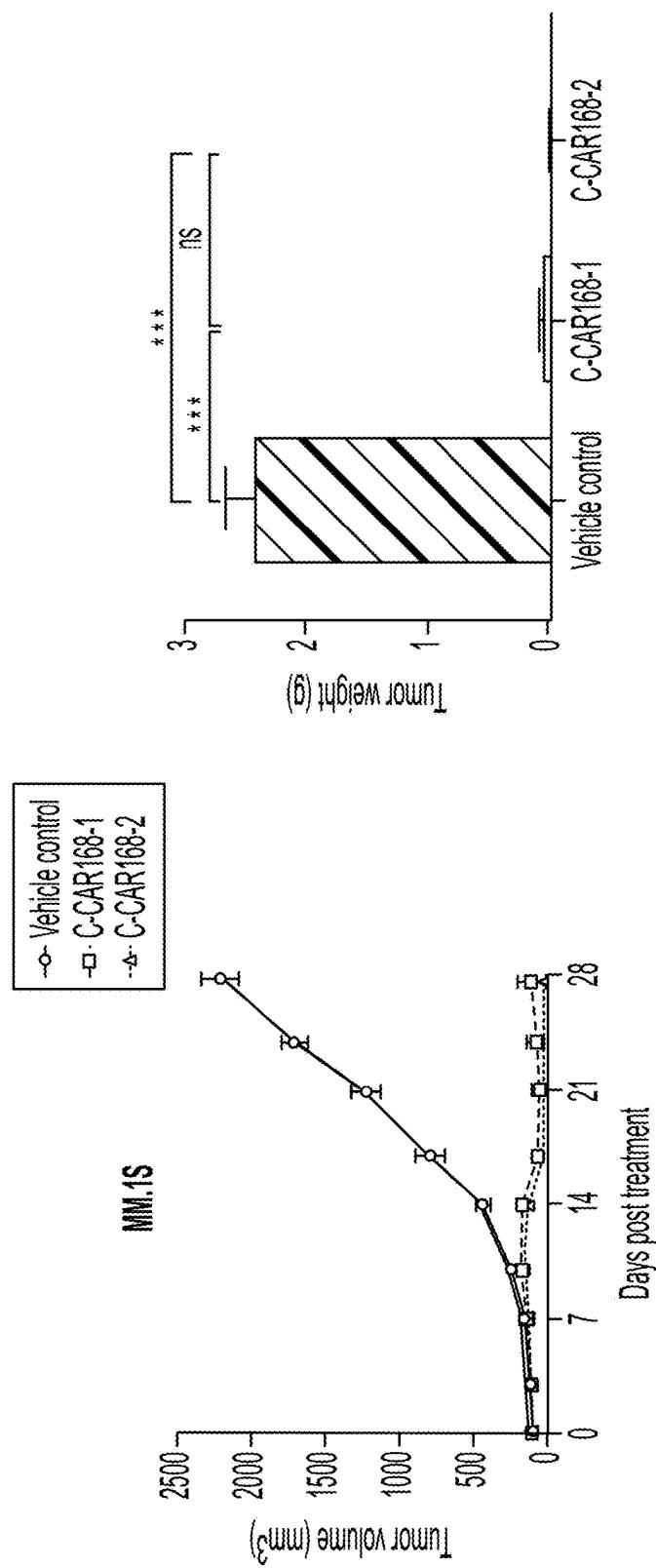


FIG. 9B

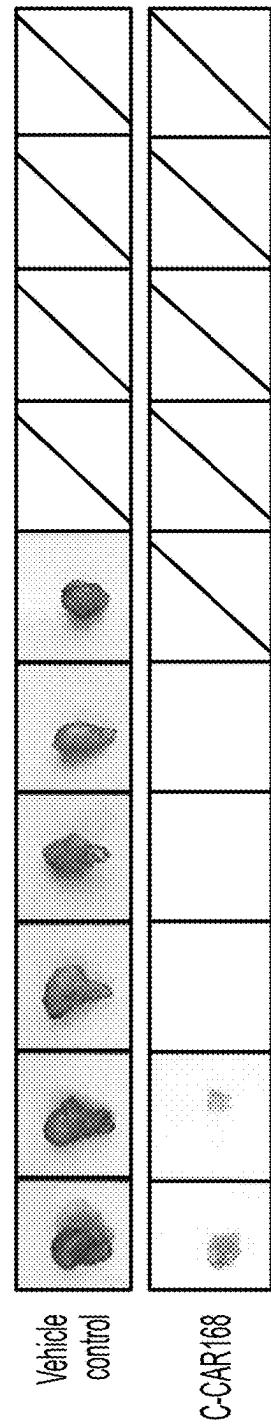


FIG. 9C

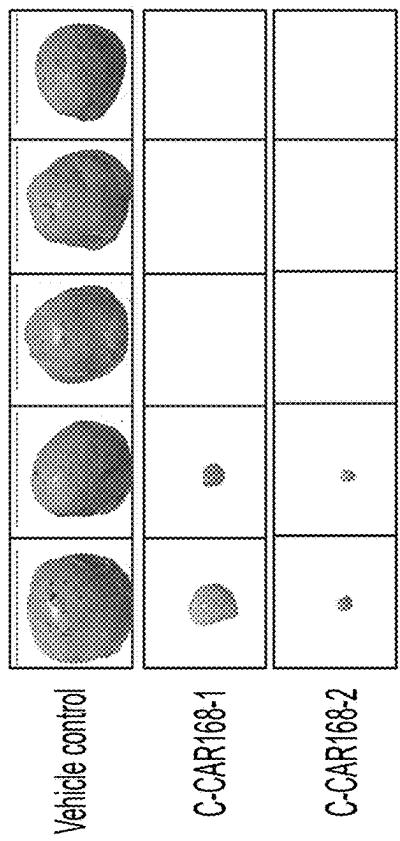


FIG. 9D

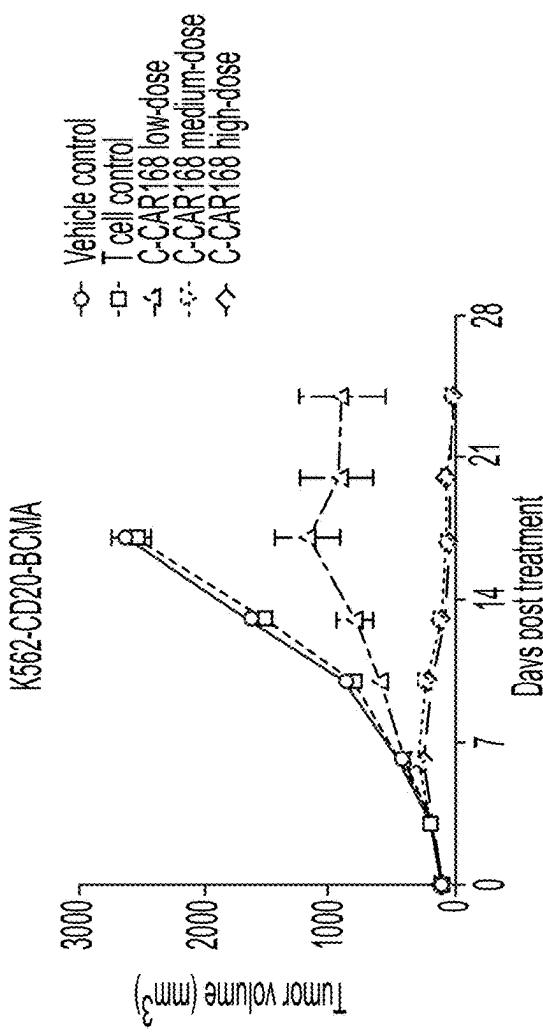


FIG. 9E

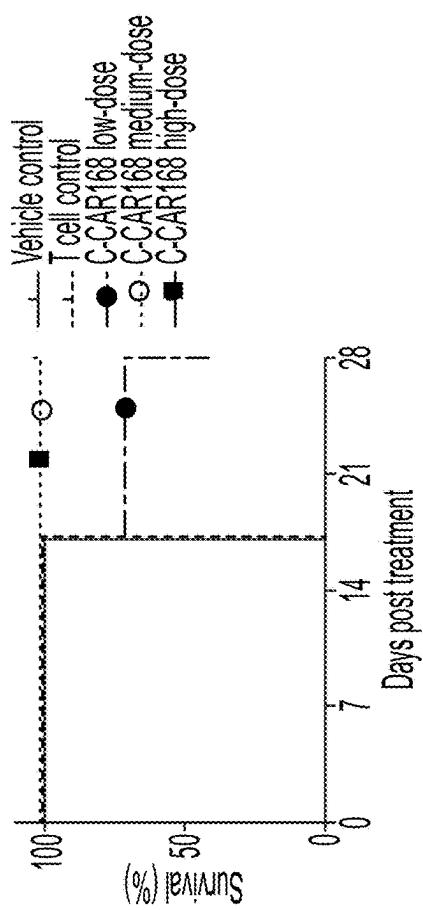


FIG. 9F

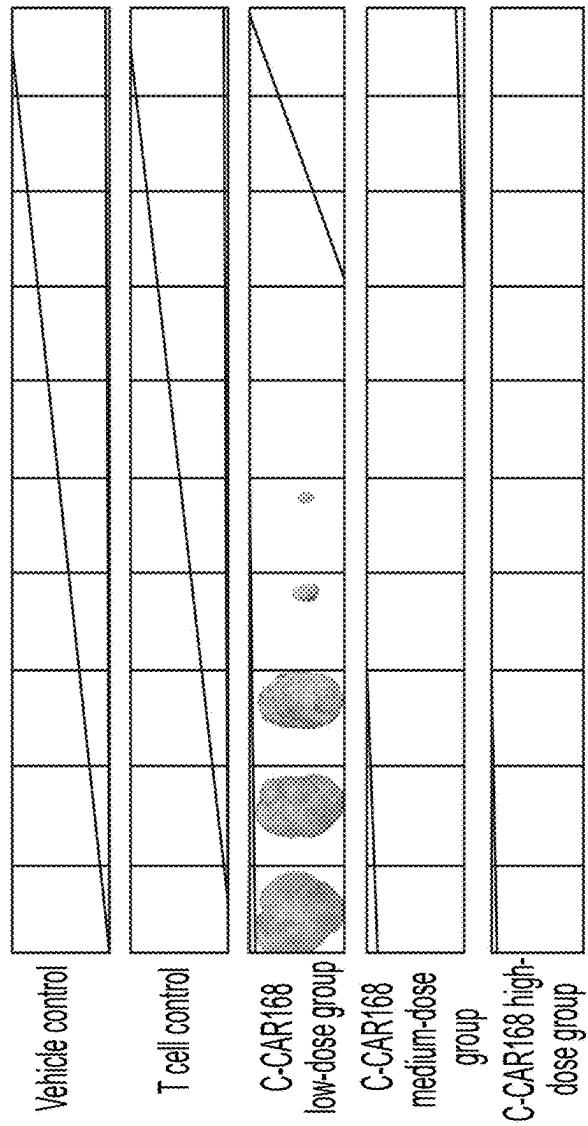


FIG. 9G

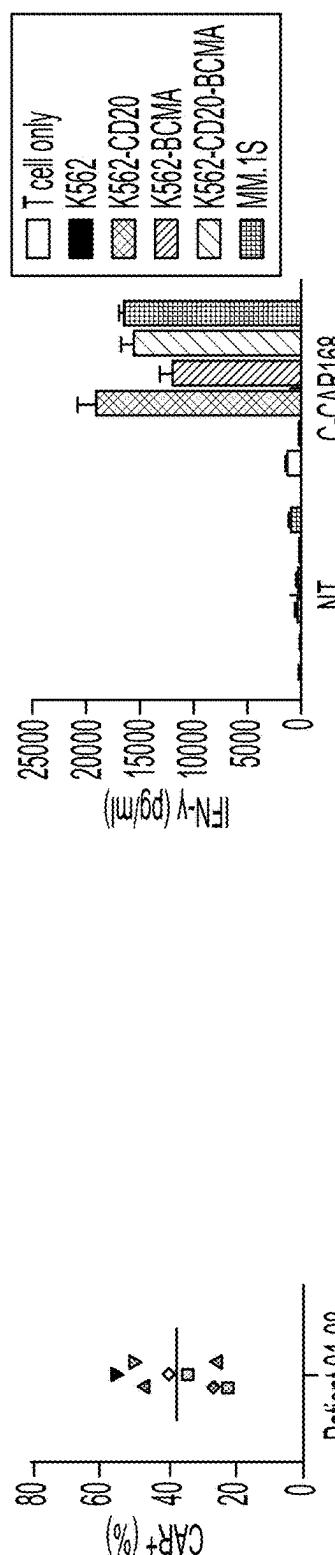
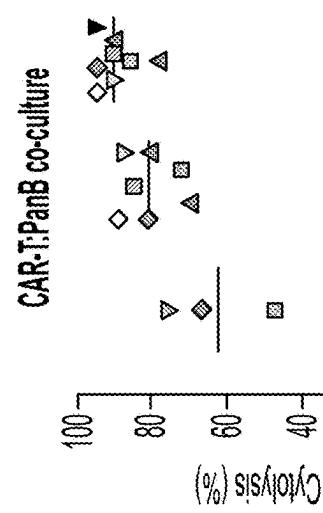
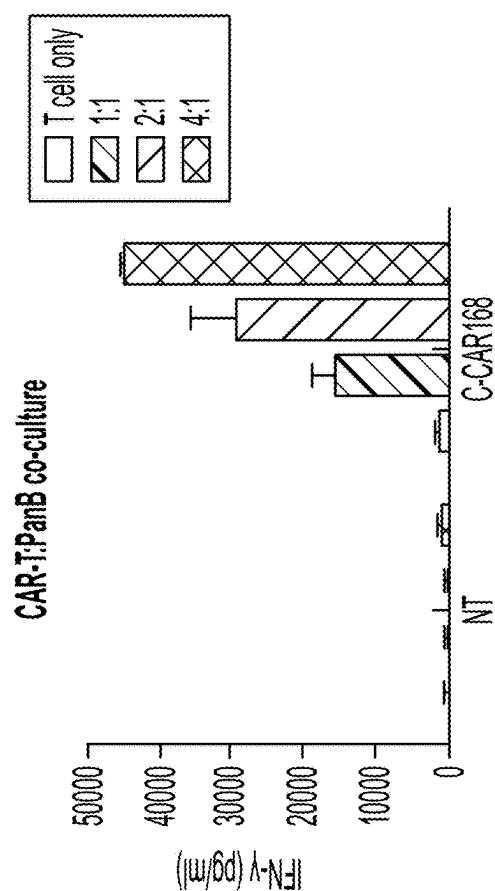
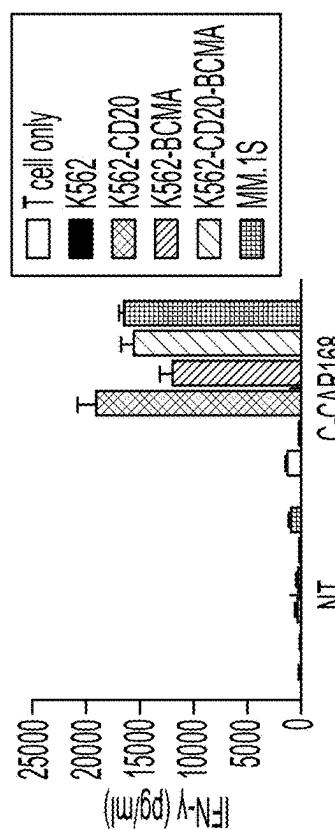


FIG. 10B



**BISPECIFIC CHIMERIC ANTIGEN
RECEPTORS TARGETING CD20 AND BCMA****CROSS REFERENCE TO RELATED
APPLICATIONS**

[0001] The present application is a continuation application of U.S. patent application Ser. No. 19/003,301 (filed on Dec. 27, 2024), which is a continuation application of PCT/US2024/022317 (filed on March 29, 2024), which claims priority to U.S. Provisional Patent Application Nos. 63/493,495 (filed on Mar. 31, 2023) and 63/509,371 (filed on Jun. 21, 2023), each of which is hereby incorporated by reference in its entirety.

**INCORPORATION-BY-REFERENCE OF
SEQUENCE LISTING**

[0002] The application contains a sequence listing which has been submitted electronically in XML format and is hereby incorporated by reference in its entirety. Said XML copy, created on Apr. 24, 2025, is named 11299_011840-US5_SL.xml and is 168,342 bytes in size.

FIELD OF THE INVENTION

[0003] The present disclosure relates to the field of immunotherapy, and more particularly to bispecific chimeric antigen receptors (CARs) targeting CD20 and BCMA.

BACKGROUND

[0004] Autoimmune diseases are conditions caused by the immune system's response to the body itself, resulting in damage to its own tissues. These are typically divided into two main categories: systemic autoimmune diseases, such as systemic lupus erythematosus (SLE), rheumatoid arthritis, and systemic vasculitis; and organ-specific autoimmune diseases, such as autoimmune hepatitis and type I diabetes. Most autoimmune diseases are difficult to cure and often require long-term or lifelong medication. Treatment primarily involves corticosteroids and immunosuppressants, greatly impacting the patient's quality of life and presenting a significant unmet clinical need (Wang et al., Human autoimmune diseases: a comprehensive update, *J. Intern. Med.* 2015, 278(4):369-95).

[0005] The etiology of autoimmune diseases is unclear. In patients, abnormal activation of humoral immunity occurs, leading to the production of a large number of antibodies against self-antigens. These combine to form pathogenic immune complexes, which then deposit locally and cause inflammatory reactions. B cells play an important role in the pathogenesis of autoimmune diseases, promoting the occurrence of autoimmune diseases through various mechanisms such as producing autoantibodies, releasing cytokines, and presenting autoantigens. Autoantibodies, as a key factor, can bind with autoantigens to form immune complexes, which can activate innate immune system cells to produce type I interferon and other pro-inflammatory cytokines resulting in organ damage. Therefore, the depletion or removal of lymphocytes has become a potential treatment strategy.

[0006] SLE is a prototypic autoimmune disease that is known to be associated with polyclonal B-cell hyperreactivity (Dorner et al., Mechanisms of B cell autoimmunity in SLE, *Arthritis Res. Ther.* 13, 243 (2011)). As such, one of the immunological hallmarks of SLE is the production of anti-nuclear antibodies (ANAs), which can mediate SLE patho-

genesis by binding to respective autoantigens, resulting in deposition of immune complexes and induction of inflammation and organ damage (for example, lupus nephritis) (Salmon, J. E., Arming T cells against B cells in systemic lupus erythematosus, *Nat. Med.* 28, 2009-2010 (2022)). There are two main types of ANAs: anti-DNA antibodies and antibodies recognizing RNA-binding proteins (RBP) (Pisetsky et al., New insights into the role of antinuclear antibodies in systemic lupus erythematosus, *Nat. Rev. Rheumatol.* 16, 565-579 (2020)). In patients with SLE, the sources of autoantibodies include not only B cells but also a subset of plasma cells termed long-lived plasma cells (LLPCs). While the anti-DNA antibodies are produced by naïve B cells that transition to memory B cells and plasmablasts, which maintain high level expression of CD19 and CD20 on the cell surface, the anti-RBP antibodies are produced by LLPCs, which may lose surface expression of CD19 and CD20, but are positive for B-cell maturation antigen (BCMA), a cell surface protein expressed on all mature plasma cells (Dogan et al., B-cell maturation antigen expression across hematologic cancers: a systematic literature review. *Blood Cancer J.* 10, 73 (2020); Morgan et al., Unraveling B cell trajectories at single cell resolution, *Trends Immunol.* 43, 210-229 (2022)). Recent studies demonstrated that a CD11c^{hi}T-bet⁺ B cell subset is expanded in human SLE and serves as precursors of autoantibody producing plasma cells. This B cell subset displays high expression of CD19 and CD20 and corresponds to the autoreactive, murine age-associated B cells (autoreactive B cells or ABCs; the term may be used to represent human CD11c^{hi}T-bet⁺ B cells) (Jenks et al., Distinct Effector B Cells Induced by Unregulated Toll-like Receptor 7 Contribute to Pathogenic Responses in Systemic Lupus Erythematosus, *Immunity* 49, 725-739 e726 (2018); Wang et al., IL-21 drives expansion and plasma cell differentiation of autoreactive CD11c(hi)T-bet(+) B cells in SLE, *Nat. Commun.* 9, 1758 (2018)). In addition to autoantibody production, B cells also participate in the pathogenesis of SLE and other autoimmune diseases by secreting cytokines and acting as antigen-presenting cells. Therefore, depleting B cells in patients with SLE can be an effective therapy for this life-threatening disease.

[0007] B cell depletion could be achieved by administration of monoclonal antibodies against B cell surface markers. Although the anti-CD20 antibody rituximab was successful in early open-label trials in SLE, it failed to meet its primary end points in two randomized controlled trials (Lee et al., B cell depletion therapies in autoimmune disease: advances and mechanistic insights, *Nat. Rev. Drug Discov.* 20, 179-199 (2021)). Other antibodies targeting CD19 (obexelimab) were also tested in SLE. Although patients receiving obexelimab sustained their level of disease inactivity despite steroid withdrawal in initial studies, phase II clinical trials, failed to meet their primary end points (Lee et al., B cell depletion therapies in autoimmune disease: advances and mechanistic insights, *Nat. Rev. Drug Discov.* 20, 179-199 (2021)).

[0008] One promising approach to achieve B cell depletion is adoptive transfer of CAR-T cells. CAR-T cells are genetically engineered T lymphocytes that, in the absence of major histocompatibility complex (MHC), can recognize specific antigens on target cells, proliferate, and generate cytotoxic immune responses. In a recent study, compassionate-use of CD19 CAR-T therapy in 5 patients with refractory SLE led to deep depletion of B cells and drug-free remis-

sion, suggesting that CAR-T cell transfer is feasible, tolerable, and highly effective in SLE (Mackensen et al., Anti-CD19 CART cell therapy for refractory systemic lupus erythematosus, Nat. Med. 28, 2124-2132 (2022)).

[0009] There is still an urgent need to develop methods to effectively treat autoimmune diseases.

SUMMARY

[0010] The present disclosure provides for a bispecific chimeric antigen receptor (CAR), comprising: (i) an anti-CD20 antigen-binding region which comprises a light chain variable region (V_L1) and a heavy chain variable region (V_H1), wherein V_L1 comprises three complementarity determining regions (CDRs), CDR1, CDR2 and CDR3, having amino acid sequences about 80% to about 100% identical to the amino acid sequences set forth in SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, respectively, and wherein V_H1 comprises three CDRs, CDR1, CDR2 and CDR3, having amino acid sequences about 80% to about 100% identical to the amino acid sequences set forth in SEQ ID NO: 127, SEQ ID NO: 128, SEQ ID NO: 129, respectively; and (ii) an anti-BCMA antigen-binding region which comprises a light chain variable region (V_L2) and a heavy chain variable region (V_H2), wherein V_L2 comprises three complementarity determining regions (CDRs), CDR1, CDR2 and CDR3, having amino acid sequences about 80% to about 100% identical to the amino acid sequences set forth in SEQ ID NO: 134, SEQ ID NO: 136, SEQ ID NO: 138, respectively, and wherein V_H2 comprises three CDRs, CDR1, CDR2 and CDR3, having amino acid sequences about 80% to about 100% identical to the amino acid sequences set forth in SEQ ID NO: 141, SEQ ID NO: 143, SEQ ID NO: 145, respectively.

[0011] The present disclosure provides for a bispecific chimeric antigen receptor (CAR), comprising: (i) an anti-CD20 antigen-binding region which comprises a light chain variable region (V_L1) and a heavy chain variable region (V_H1); and (ii) an anti-BCMA antigen-binding region which comprises a light chain variable region (V_L2) and a heavy chain variable region (V_H2).

[0012] In one embodiment, V_L1 is located at the N-terminus of V_H1 . In one embodiment, V_H1 is located at the N-terminus of V_L1 . In one embodiment, V_L2 is located at the N-terminus of V_H2 . In one embodiment, V_H2 is located at the N-terminus of V_L2 .

[0013] In certain embodiments, V_L1 and V_H1 have amino acid sequences about 80% to about 100% identical to amino acid sequences set forth in SEQ ID NO: 4 and SEQ ID NO: 8, respectively.

[0014] In certain embodiments, V_L2 and V_H2 have amino acid sequences about 80% to about 100% identical to amino acid sequences set forth in SEQ ID NO: 12 and SEQ ID NO: 16, respectively.

[0015] The anti-CD20 antigen-binding region may be a single-chain variable fragment (scFv) that specifically binds CD20. The anti-BCMA antigen-binding region may be a scFv that specifically binds BCMA.

[0016] The bispecific CAR may further comprise one or more of the following: (a) a signal peptide, (b) a hinge region, (c) a transmembrane domain, (d) a co-stimulatory region, and (e) a cytoplasmic signaling domain.

[0017] The hinge region may comprise a hinge region of IgG4, CD8, CD28, CD137, or combinations thereof.

[0018] The transmembrane domain may comprise a transmembrane domain of CD8, CD28, CD3 ϵ , CD45, CD4, CD5, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137, CD154, or combinations thereof.

[0019] The co-stimulatory region may comprise a co-stimulatory region of 4-1BB (CD137), CD28, OX40, CD2, CD7, CD27, CD30, CD40, CD70, CD134, PD1, Dap10, CDS, ICAM-1, LFA-1 (CD11a/CD18), ICOS (CD278), NKG2D, GITR, TLR2, or combinations thereof.

[0020] The cytoplasmic signaling domain may comprise a cytoplasmic signaling domain of CD3 ζ .

[0021] The present disclosure provides for a bispecific CAR comprising (or having) an amino acid sequence about 80% to about 100% identical to the amino acid sequence set forth in SEQ ID NO:26, SEQ ID NO:40, SEQ ID NO:54, SEQ ID NO:68, SEQ ID NO:84, SEQ ID NO:98, SEQ ID NO:112, or SEQ ID NO:126.

[0022] Also encompassed by the present disclosure is an immune cell expressing the bispecific CAR. The immune cell may be a T cell or a natural killer (NK) cell.

[0023] The present disclosure provides for a nucleic acid encoding the bispecific CAR.

[0024] The present disclosure provides for a vector comprising the present nucleic acid encoding the bispecific CAR.

[0025] The present disclosure provides for a pharmaceutical composition comprising the bispecific CAR, the immune cell, the nucleic acid, or the vector.

[0026] The present disclosure also provides for a method of treating an autoimmune disorder. The method may comprise administering the immune cell, or the pharmaceutical composition, to a subject in need thereof.

[0027] The autoimmune disorder may be systemic lupus erythematosus (SLE) (e.g., lupus nephritis), systemic vasculitis, systemic sclerosis, inflammatory myopathy (e.g., polymyositis, dermatomyositis, or inclusion-body myositis), systemic scleroderma, multiple sclerosis, myasthenia gravis, a myositis autoantibody-driven disease, or neuromyelitis optica.

[0028] The autoimmune disorder may be polymyositis, dermatomyositis, or inclusion-body myositis. The autoimmune disorder may be lupus nephritis.

[0029] The present disclosure also provides for a method of treating a cancer. The method may comprise administering the immune cell, or the pharmaceutical composition, to a subject in need thereof.

[0030] The cancer may be a hematologic cancer. The cancer may be a B-cell malignancy. The cancer may be Hodgkin's lymphoma, non-Hodgkin's lymphoma, leukemia, and/or multiple myeloma. The cancer may be acute myeloid leukemia (AML), multiple myeloma (MM), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia, acute lymphoblastic leukemia (ALL), diffuse large B cell lymphoma (DLBCL), or combinations thereof.

[0031] The immune cell may be allogeneic or autologous.

BRIEF DESCRIPTION OF THE DRAWINGS

[0032] FIG. 1 shows the structures of the combined chimeric antigen receptors targeting CD20 and BCMA. The structures of the CARs include a signal peptide (SP), an anti-CD20 scFv (OF), a linker (linker-2), an anti-BCMA scFv (B20), a hinge region, a transmembrane domain, a co-stimulatory region, and a cytoplasmic signaling domain (CD3 ζ). A short IgG4 hinge (12 aa) and a CD28 transmem-

brane domain are included in TOB1 to TOB4; a CD8a hinge and a CD8a transmembrane domain are included in TOBL1 to TOBL4. Four combinations of orientations of V_H and V_L in the two scFv sequences are included in the two groups of CARs (TOB1-4 and TOBL1-4). TOBL1 is also named C-CAR168.

[0033] FIG. 2 shows the expression level of anti-CD20 and anti-BCMA CARs on the surface of the T cells.

[0034] FIGS. 3A-3C show the levels of IFN- γ secreted by the activated CAR-T cells in vitro in the cell culture supernatant. FIG. 3A shows the levels of IFN- γ secreted by the TOB1 to TOB4 CAR-T cells in the cell culture supernatant. FIG. 3B shows the levels of IFN- γ secreted by the TOBL1 to TOBL4 CAR-T cells in the cell culture supernatant. FIG. 3C: TOBL1 to TOBL4 showed high level IFN- γ release when co-cultured with target cells naturally expressing CD20 and BCMA. MM.1S is a BCMA-positive multiple myeloma (MM) cell line; RAJI is CD20 positive and BCMA positive.

[0035] FIGS. 4A-4B show the expression levels of CD137 on the surface of the activated CAR-T cells.

[0036] FIGS. 5A-5B show the in vitro cytotoxicity of CAR-Ts cells (FIG. 5A: TOB1 to TOB4; FIG. 5B: TOBL1 to TOBL4) by RTCA assays.

[0037] FIGS. 6A-6C: C-CAR168 shows robust potency against CD20+ and BCMA+ cells in vitro. FIG. 6A shows the structures of C-CAR168 (TOBL1 which is an anti-CD20/BCMA CAR), anti-CD20 CAR (C-CAR066), and anti-BCMA CAR (C-CAR088). FIG. 6B shows the release of IFN- γ after the CAR-T cells were co-cultured with CD20-positive and/or BCMA-positive target cells. FIG. 6C shows the cytotoxicity of the CAR-T cells targeting CD20 and/or BCMA, at different E:T ratios.

[0038] FIGS. 7A-7C: Cytotoxicity of C-CAR168 on ABC-enriched B cells in vitro. FIG. 7A: Generation of C-CAR168 CAR-T cells. The lower panels show the CAR positive rate of C-CAR168 CAR-T cells prepared from the peripheral blood of 3 healthy donors. FIG. 7B: Differentiation of ABCs. The lower panels show that the proportion of ABC subpopulations increased significantly after induction of differentiation of autologous B cells. FIG. 7C: Cytolysis of ABC-enriched B cells by C-CAR168 at different E:T ratios.

[0039] FIGS. 8A-8D: C-CAR168 bears no cross-reactivity against human membrane proteome. FIGS. 8A-8B: C-CAR168 scFv-RabFc binding specificity in the membrane protein array. FIG. 8C: Flow cytometry detection of expression of ITGB2-ITGAM and ITGB2-ITGAL in 293T cells.

[0040] FIG. 8D (left panel): Flow cytometric detection of the proportion of 4-1BB-positive cells. FIG. 8D (right panel): Flow cytometry detection of IFN- γ concentrations in the co-culture supernatants.

[0041] FIGS. 9A-9G: In vivo cytotoxicity of C-CAR168 in tumor-bearing mice. FIG. 9A: C-CAR168 significantly inhibited the growth of A549-CD20 cells in B-NDG tumor bearing mice. Left panel: tumor growth curve of each group during the experiment; right panel: average tumor weight of animals in each group at Day 42. ***: P<0.001, compared to the vehicle control group. FIG. 9B: C-CAR168 significantly inhibited the growth of human multiple myeloma MM.1S tumor cells in B-NDG tumor bearing mice. Left panel: tumor growth curve of each group during the experiment; right panel: average tumor weight of animals in each group at Day 28. ***: P<0.001, compared to the vehicle control group. FIG. 9C: Images of the A549-CD20 tumors of

the animals in each group at Day 42. “/” indicates that the animal was dead. The blank box indicates that no tumor tissue was collected. FIG. 9D: Images of MM.1S tumors of the animals in each group at Day 28. The blank box indicates that no tumor tissue was collected. FIGS. 9E-9G: C-CAR168 significantly inhibited the growth of K562-CD20-BCMA tumor cells in B-NDG tumor bearing mice. FIG. 9E: Tumor growth curve of each group during the experiment. FIG. 9F: The survival rate curve of each group during the experimental period. FIG. 9G: Images of tumors of animals in each group at Day 28. “/” indicates that the animal was dead. The blank box indicates that no tumor tissue was collected.

[0042] FIGS. 10A-10D: C-CAR168 shows robust potency in vitro against autologous B cells from SLE patients. FIG. 10A: T cells from eight SLE patients were successfully transduced by lentiviral vectors encoding C-CAR168 and expressed the anti-CD20/BCMA CAR. FIG. 10B: C-CAR168 CAR-T cells generated from the SLE patient samples showed robust activity (IFN- γ release) against target cells expressing CD20 and BCMA. K562 is negative for both CD20 and BCMA; MM.1S is a multiple myeloma cell line which is BCMA-positive. FIG. 10C: C-CAR168 CAR-T cells generated from the SLE patient samples showed robust activity (e.g., IFN- γ release) against pan B cells isolated from the SLE patients. FIG. 10D: Pan B cells isolated from the SLE patients were recognized and lysed by autologous C-CAR168 cells.

DETAILED DESCRIPTION

[0043] The present disclosure provides a chimeric antigen receptor (CAR) that targets both CD20 and BCMA. The CAR may comprise a signal peptide, an anti-CD20 scFv, an anti-BCMA scFv, a hinge region, a transmembrane domain, a co-stimulatory region, and a cytoplasmic signaling domain. The present CARs can be used to treat autoimmune diseases or cancer.

[0044] B-cell maturation antigen (BCMA), also known as TNFRSF17 or CD269, is a member of the tumor necrosis factor receptor family. It serves as an important receptor for B-cell activating factor (BAFF), along with TACI and BAFF-R, and participates in the regulation of B lymphocyte differentiation and maturation. BCMA is a type III transmembrane protein, specifically expressed in B cells, especially in plasmablasts and differentiated mature plasma cells.

[0045] CD20, which is a B-cell membrane marker, also known as B1, is a transmembrane glycoprotein encoded by the MS4A gene. CD20 plays an important role in the development, proliferation, activation, differentiation, and malignant transformation of B cells through the regulation of transmembrane Ca^{2+} conductance.

[0046] The present disclosure provides for a bispecific chimeric antigen receptor (CAR). The bispecific CAR may comprise: (i) an anti-CD20 antigen-binding region which comprises a light chain variable region (V_L 1) and a heavy chain variable region (V_H 1); and (ii) an anti-BCMA antigen-binding region which comprises a light chain variable region (V_L 2) and a heavy chain variable region (V_H 2).

[0047] The present bispecific chimeric antigen receptor (CAR) may comprise: (i) an anti-CD20 antigen-binding region which comprises a light chain variable region (V_L 1) having amino acid sequences about 80% to about 100%, about 85% to about 100%, about 90% to about 100%, or about 95% to about

100%, identical to the amino acid sequences set forth in SEQ ID NO: 4 and SEQ ID NO: 8, respectively; and (ii) an anti-BCMA antigen-binding region which comprises a light chain variable region (V_L2) and a heavy chain variable region (V_H2) having amino acid sequences about 80% to about 100%, about 85% to about 100%, about 90% to about 100%, or about 95% to about 100%, identical to the amino acid sequences set forth in SEQ ID NO: 12 and SEQ ID NO: 16, respectively.

[0048] The present disclosure provides for a bispecific chimeric antigen receptor (CAR). The bispecific CAR may comprise: (i) an anti-CD20 antigen-binding region which comprises a light chain variable region (V_L1) and a heavy chain variable region (V_H1), and (ii) an anti-BCMA antigen-binding region which comprises a light chain variable region (V_L2) and a heavy chain variable region (V_H2). V_L1 may comprise three complementarity determining regions (CDRs), CDR1, CDR2 and CDR3, having amino acid sequences about 80% to about 100%, about 85% to about 100%, about 90% to about 100%, or about 95% to about 100%, identical to the amino acid sequences set forth in SEQ ID NO: 127, SEQ ID NO: 128, SEQ ID NO: 129, respectively. V_L2 may comprise three complementarity determining regions (CDRs), CDR1, CDR2 and CDR3, having amino acid sequences about 80% to about 100%, about 85% to about 100%, about 90% to about 100%, or about 95% to about 100%, identical to the amino acid sequences set forth in SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, respectively. V_H1 may comprise three CDRs, CDR1, CDR2 and CDR3, having amino acid sequences about 80% to about 100%, about 85% to about 100%, about 90% to about 100%, or about 95% to about 100%, identical to the amino acid sequences set forth in SEQ ID NO: 134, SEQ ID NO: 136, SEQ ID NO: 138, respectively. V_H2 may comprise three CDRs, CDR1, CDR2 and CDR3, having amino acid sequences about 80% to about 100%, about 85% to about 100%, about 90% to about 100%, or about 95% to about 100%, identical to the amino acid sequences set forth in SEQ ID NO: 141, SEQ ID NO: 143, SEQ ID NO: 145, respectively.

[0049] In certain embodiments, V_L1 is located at the N-terminus of V_H1 . In certain embodiments, V_H1 is located at the N-terminus of V_L1 . In certain embodiments, V_H2 is located at the N-terminus of V_L2 . In certain embodiments, V_L2 is located at the N-terminus of V_H2 . In one embodiment, V_L1 is located at the N-terminus of V_H1 ; V_L2 is located at the N-terminus of V_H2 .

[0050] In certain embodiments, V_L1 and V_H1 have amino acid sequences about 80% to about 100% identical to amino acid sequences set forth in SEQ ID NO: 4 and SEQ ID NO: 8, respectively.

[0051] In certain embodiments, V_L2 and V_H2 have amino acid sequences about 80% to about 100% identical to amino acid sequences set forth in SEQ ID NO: 12 and SEQ ID NO: 16, respectively.

[0052] In certain embodiments, the antigen-binding region that specifically binds CD20 is located at the N-terminus of the antigen-binding region that specifically binds BCMA. In certain embodiments, the antigen-binding region that specifically binds BCMA is located at the N-terminus of the antigen-binding region that specifically binds CD20.

[0053] The anti-CD20 antigen-binding region may be a single-chain variable fragment (scFv) that specifically binds CD20. The anti-BCMA antigen-binding region may be a

scFv that specifically binds BCMA. In certain embodiments, the scFv that specifically binds CD20 is located at the N-terminus of the scFv that specifically binds BCMA. In certain embodiments, the scFv that specifically binds BCMA is located at the N-terminus of the scFv that specifically binds CD20.

[0054] The bispecific CAR may further comprise one or more of the following: (a) a signal peptide or SP (or a leader sequence), (b) a hinge region, (c) a transmembrane domain, (d) a co-stimulatory region, and (e) a cytoplasmic signaling domain.

[0055] The present bispecific CARs may comprise, from N-terminus to C-terminus, a signal peptide, an anti-CD20 scFv, an anti-BCMA scFv, a hinge region, a transmembrane domain, and a co-stimulatory region, and a cytoplasmic signaling domain.

[0056] The signal peptide may comprise a signal peptide of (or may be derived from) CD8, CD28, GM-CSF, CD4, CD137, or combinations thereof. In one embodiment, the signal peptide is a signal peptide of (or is derived from) CD8.

[0057] In one embodiment, the signal peptide comprises an amino acid sequence about 80% to about 100%, about 85% to about 100%, about 90% to about 100%, or about 95% to about 100%, identical to the amino acid sequence set forth in SEQ ID NO: 2.

[0058] The hinge region may comprise a hinge region of (or may be derived from) IgG4, CD8, CD28, CD137, or combinations thereof, wildtype or mutants.

[0059] In one embodiment, the hinge region is a hinge region of (or is derived from) IgG4. In one embodiment, the hinge region comprises an amino acid sequence about 80% to about 100%, about 85% to about 100%, about 90% to about 100%, or about 95% to about 100%, identical to the amino acid sequence set forth in SEQ ID NO: 78.

[0060] In one embodiment, the hinge region is a hinge region of (or is derived from) CD8a. In one embodiment, the hinge region comprises an amino acid sequence about 80% to about 100%, about 85% to about 100%, about 90% to about 100%, or about 95% to about 100%, identical to the amino acid sequence set forth in SEQ ID NO: 18.

[0061] The transmembrane domain may comprise a transmembrane domain of (or may be derived from) CD8, CD28, CD3s, CD45, CD4, CD5, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137, CD154, or combinations thereof.

[0062] In one embodiment, the transmembrane domain is a transmembrane domain of (or is derived from) CD8. In one embodiment, the transmembrane domain comprises an amino acid sequence about 80% to about 100%, about 85% to about 100%, about 90% to about 100%, or about 95% to about 100%, identical to the amino acid sequence set forth in SEQ ID NO: 20.

[0063] In one embodiment, the transmembrane domain is a transmembrane domain of (or is derived from) CD28. In one embodiment, the transmembrane domain comprises an amino acid sequence about 80% to about 100%, about 85% to about 100%, about 90% to about 100%, or about 95% to about 100%, identical to the amino acid sequence set forth in SEQ ID NO: 80.

[0064] The co-stimulatory region may comprise a co-stimulatory region of (or may be derived from) 4-1BB (CD137), CD28, OX40, CD2, CD7, CD27, CD30, CD40,

CD70, CD134, PD1, Dap10, CDS, ICAM-1, LFA-1 (CD11a/CD18), ICOS (CD278), NKG2D, GITR, TLR2, or combinations thereof.

[0065] In one embodiment, the co-stimulatory region is a co-stimulatory region of (or is derived from) 4-1BB. In one embodiment, the co-stimulatory region comprises an amino acid sequence about 80% to about 100%, about 85% to about 100%, about 90% to about 100%, or about 95% to about 100%, identical to the amino acid sequence set forth in SEQ ID NO: 22.

[0066] The cytoplasmic signaling domain may comprise a cytoplasmic signaling domain of (or may be derived from) CD3 ζ . In one embodiment, the cytoplasmic signaling domain comprises an amino acid sequence about 80% to about 100%, about 85% to about 100%, about 90% to about 100%, or about 95% to about 100%, identical to the amino acid sequence set forth in SEQ ID NO: 24.

[0067] The present CAR may comprise a linker (linker-1) between V_L and V_H of the anti-CD20 antigen-binding region. In one embodiment, the linker (linker-1) comprises an amino acid sequence about 80% to about 100%, about 85% to about 100%, about 90% to about 100%, or about 95% to about 100%, identical to the amino acid sequence set forth in SEQ ID NO:6.

[0068] The present CAR may comprise a linker (linker-2) between the anti-CD20 antigen-binding region and the anti-BCMA antigen-binding region. In one embodiment, the linker (linker-2) comprises an amino acid sequence about 80% to about 100%, about 85% to about 100%, about 90% to about 100%, or about 95% to about 100%, identical to the amino acid sequence set forth in SEQ ID NO:10.

[0069] The present CAR may comprise a linker (linker-3) between V_L and V_H of the anti-BCMA antigen-binding region. In one embodiment, the linker (linker-3) comprises an amino acid sequence about 80% to about 100%, about 85% to about 100%, about 90% to about 100%, or about 95% to about 100%, identical to the amino acid sequence set forth in SEQ ID NO:14.

[0070] In one embodiment, the bispecific CAR comprises, from N-terminus to C-terminus, (a) an anti-CD20 antigen-binding region with a light chain variable region (V_L1) and a heavy chain variable region (V_H1) of those of ofatumumab, (ii) an anti-BCMA antigen-binding region with a light chain variable region (V_L2) and a heavy chain variable region (V_H2) of those of the BCMA-20 antibody, (iii) a hinge region having an amino acid sequence set forth in SEQ ID NO:18, (iv) a transmembrane domain having an amino acid sequence set forth in SEQ ID NO:20, (v) a co-stimulatory region having an amino acid sequence set forth in SEQ ID NO:22, and (vi) a cytoplasmic signaling domain having an amino acid sequence set forth in SEQ ID NO:24.

[0071] In one embodiment, the bispecific CAR comprises, from N-terminus to C-terminus, (a) an anti-CD20 antigen-binding region with a light chain variable region (V_L1) and a heavy chain variable region (V_H1) having amino acid sequences set forth in SEQ ID NO:4 and SEQ ID NO:8, respectively, (ii) an anti-BCMA antigen-binding region with a light chain variable region (V_L2) and a heavy chain variable region (V_H2) having amino acid sequences set forth in SEQ ID NO:12 and SEQ ID NO:16, respectively, (iii) a hinge region having an amino acid sequence set forth in SEQ ID NO:18, (iv) a transmembrane domain having an amino acid sequence set forth in SEQ ID NO:20, (v) a co-stimulatory region having an amino acid sequence set forth in SEQ ID NO:22, (vi) a cytoplasmic signaling domain having an amino acid sequence set forth in SEQ ID NO:24.

SEQ ID NO:22, and (vi) a cytoplasmic signaling domain having an amino acid sequence set forth in SEQ ID NO:24.

[0072] In one embodiment, the bispecific CAR comprises, from N-terminus to C-terminus, (a) an anti-CD20 antigen-binding region with a light chain variable region (V_L1) and a heavy chain variable region (V_H1) of those of ofatumumab, (ii) an anti-BCMA antigen-binding region with a light chain variable region (V_L2) and a heavy chain variable region (V_H2) of those of BCMA-20, (iii) a hinge region having an amino acid sequence set forth in SEQ ID NO:78, (iv) a transmembrane domain having an amino acid sequence set forth in SEQ ID NO:80, (v) a co-stimulatory region having an amino acid sequence set forth in SEQ ID NO:22, and (vi) a cytoplasmic signaling domain having an amino acid sequence set forth in SEQ ID NO:24.

[0073] In one embodiment, the bispecific CAR comprises, from N-terminus to C-terminus, (a) an anti-CD20 antigen-binding region with a light chain variable region (V_L1) and a heavy chain variable region (V_H1) having amino acid sequences set forth in SEQ ID NO:4 and SEQ ID NO:8, respectively, (ii) an anti-BCMA antigen-binding region with a light chain variable region (V_L2) and a heavy chain variable region (V_H2) having amino acid sequences set forth in SEQ ID NO:12 and SEQ ID NO:16, respectively, (iii) a hinge region having an amino acid sequence set forth in SEQ ID NO:78, (iv) a transmembrane domain having an amino acid sequence set forth in SEQ ID NO:80, (v) a co-stimulatory region having an amino acid sequence set forth in SEQ ID NO:22, and (vi) a cytoplasmic signaling domain having an amino acid sequence set forth in SEQ ID NO:24.

[0074] In certain embodiments, V_L1 is located at the N-terminus of V_H1. In certain embodiments, V_H1 is located at the N-terminus of V_L1. In certain embodiments, V_H2 is located at the N-terminus of V_L2. In certain embodiments, V_L2 is located at the N-terminus of V_H2. In one embodiment, V_L1 is located at the N-terminus of V_H1; V_L2 is located at the N-terminus of V_H2.

[0075] In certain embodiments, the bispecific CAR comprises an amino acid sequence about 80% to about 100%, about 85% to about 100%, about 90% to about 100%, or about 95% to about 100%, identical to the amino acid sequence set forth in SEQ ID NO:26, SEQ ID NO:40, SEQ ID NO:54, SEQ ID NO:68, SEQ ID NO:84, SEQ ID NO:98, SEQ ID NO:112, or SEQ ID NO:126.

[0076] In certain embodiments, the bispecific CAR may have an amino acid sequence set forth in SEQ ID NO:26, SEQ ID NO:40, SEQ ID NO:54, SEQ ID NO:68, SEQ ID NO:84, SEQ ID NO:98, SEQ ID NO:112, or SEQ ID NO:126.

[0077] The present bispecific CAR may be encoded by a nucleic acid having a nucleotide sequence about 80% to about 100%, about 85% to about 100%, about 90% to about 100%, or about 95% to about 100%, identical to the nucleotide sequence set forth in SEQ ID NO:25, SEQ ID NO:39, SEQ ID NO:53, SEQ ID NO:67, SEQ ID NO:83, SEQ ID NO:97, SEQ ID NO:111, or SEQ ID NO:125.

[0078] The present bispecific CAR may be encoded by a nucleic acid having a nucleotide sequence set forth in SEQ ID NO:25, SEQ ID NO:39, SEQ ID NO:53, SEQ ID NO:67, SEQ ID NO:83, SEQ ID NO:97, SEQ ID NO:111, or SEQ ID NO:125.

[0079] The present disclosure provides for an immune cell expressing or comprising the present bispecific CAR. The immune cell may be a T cell or a natural killer (NK) cell.

[0080] The present disclosure provides an immune cell, comprising the vector or the nucleic acid encoding the present CAR (e.g., integrated into its genome). The cell may be an isolated cell. The cell may be a genetically engineered cell. The cell may be a mammalian cell. In one embodiment, the cell is a CAR-T cell and/or a CAR-NK cell.

[0081] Also encompassed by the present disclosure is a nucleic acid encoding the present chimeric antigen receptor (e.g., the present bispecific CAR).

[0082] The present nucleic acid may comprise a nucleotide sequence about 80% to about 100%, about 85% to about 100%, about 90% to about 100%, or about 95% to about 100%, identical to the nucleotide sequence set forth in SEQ ID NO:25, SEQ ID NO:39, SEQ ID NO:53, SEQ ID NO:67, SEQ ID NO:83, SEQ ID NO:97, SEQ ID NO:111, or SEQ ID NO:125.

[0083] The present nucleic acid may comprise a nucleotide sequence set forth in SEQ ID NO:25, SEQ ID NO:39, SEQ ID NO:53, SEQ ID NO:67, SEQ ID NO:83, SEQ ID NO:97, SEQ ID NO:111, or SEQ ID NO:125.

[0084] The present disclosure provides for a vector comprising the present nucleic acid. The vector may comprise DNA or RNA. The vector may be a plasmid, virus vector, transposon, or combinations thereof. The vector may comprise a DNA virus or a retroviral vector. The vector may be a lentiviral vector, an adenoviral vector, an adeno-associated viral vector, or combinations thereof. In one embodiment, the vector is a lentiviral vector.

[0085] The present disclosure also provides for a pharmaceutical composition, comprising the present chimeric antigen receptor (e.g., the present bispecific CAR), the present immune cell, the present nucleic acid, or the present vector. The pharmaceutical composition may further comprise a pharmaceutically acceptable carrier, diluent or excipient. The pharmaceutical composition may be a liquid preparation.

[0086] The pharmaceutical composition may comprise the present immune cells at a concentration ranging from about 1×10^3 cells/mL to about 1×10^8 cells/mL, or from about 1×10^4 cells/mL to about 1×10^7 cells/mL.

[0087] The present disclosure also provides for a method of treating an autoimmune disease/disorder. The present disclosure provides for a method of treating cancer. The method may comprise administering the present immune cell or present pharmaceutical composition to a subject in need thereof.

[0088] The immune cell may be allogeneic or autologous.

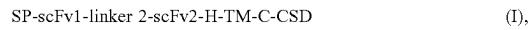
[0089] The autoimmune disorder may be systemic lupus erythematosus (SLE) (e.g., lupus nephritis), systemic sclerosis (SSc), inflammatory myopathy (e.g., polymyositis, dermatomyositis, or inclusion-body myositis), systemic scleroderma, multiple sclerosis, or neuromyelitis optica (NMO).

[0090] The cancer may be a hematologic cancer. The cancer may be a B-cell malignancy. The cancer may be Hodgkin's lymphoma, non-Hodgkin's lymphoma, leukemia, and/or multiple myeloma. The cancer may be acute myeloid leukemia (AML), multiple myeloma (MM), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia, acute lymphoblastic leukemia (ALL), diffuse large B cell lymphoma (DLBCL), or combinations thereof.

[0091] The present disclosure provides a method for preparing an immune cell (e.g., a CAR-T cell) expressing the chimeric antigen receptor, where the method comprises:

transducing the present nucleic acid molecule or the present vector into an immune cell (e.g., a T cell or NK cell), thereby obtaining the immune cell expressing the chimeric antigen receptor (e.g., the CAR-T cell).

[0092] The present disclosure provides a chimeric antigen receptor (CAR), wherein the structure of the chimeric antigen receptor may be shown in formula I:



[0093] where, each “-” is independently a linker peptide or a peptide bond; SP is an optional signal peptide; H is an optional hinge region; TM is a transmembrane domain; C is a co-stimulatory region; CSD is a cytoplasmic signaling domain; one of scFv1 and scFv2 is an anti-CD20 antigen binding region, and the other is an anti-BCMA antigen binding region.

[0094] In one embodiment, scFv1 is an anti-CD20 antigen binding region, and scFv2 is an anti-BCMA antigen binding region. In another embodiment, scFv1 is an anti-BCMA antigen binding region, and scFv2 is an anti-CD20 antigen binding region.

[0095] The structure of the anti-CD20 antigen binding region may be as shown in formula A or B as below:



wherein V_{H1} is an anti-CD20 antibody heavy chain variable region; V_{L1} is an anti-CD20 antibody light chain variable region; and “-” is a linker peptide or a peptide bond.

[0096] In one embodiment, the present CAR has an anti-CD20 antigen binding region (or domain) with a structure as shown in formula B.

[0097] In certain embodiments, the amino acid sequence of V_{L1} is shown in SEQ ID NO: 4, and the amino acid sequence of V_{H1} is shown in SEQ ID NO: 8.

[0098] V_{L1} and V_{H1} may be linked with a linker peptide (linker 1 or linker-1). Linker-1 may have the sequence set forth in SEQ ID NO: 6.

[0099] The structure of the anti-BCMA antigen binding region may be as shown in formula C or D as below:



where V_{L2} is an anti-BCMA antibody light chain variable region; V_{H2} is an anti-BCMA antibody heavy chain variable region; and “-” is a linker peptide or a peptide bond.

[0100] In one embodiment, the present CAR has an anti-BCMA antigen binding domain with a structure as shown in formula C.

[0101] In certain embodiments, the amino acid sequence of the V_{L2} is shown in SEQ ID NO: 12, and the amino acid sequence of the V_{H2} is shown in SEQ ID NO: 16.

[0102] V_{L2} and V_{H2} may be linked with a linker peptide (linker 3 or linker-3). Linker-3 may have the sequence set forth in SEQ ID NO: 14.

[0103] In another embodiment, the structure of the chimeric antigen receptor is shown in formula II as below:



[0104] In one embodiment, linker 2 (or linker-2) has the sequence set forth in SEQ ID NO: 10.

[0105] In certain embodiments, the anti-CD20 antigen-binding region includes a light chain variable region (V_L)

Ofatumumab antibody), and a heavy chain variable region (V_H) of the anti-CD20 antigen-binding region includes three CDRs that are identical to CDR1, CDR2 and CDR3 as set forth in position 30-35, position 50-66, position 99-111 of SEQ ID NO: 8 (CDRs of a heavy chain variable region of the Ofatumumab antibody).

[0114] In certain embodiments, a light chain variable region (V_L) of the anti-CD20 antigen-binding region includes three CDRs, CDR1, CDR2 and CDR3, that are identical to CDR1, CDR2 and CDR3 as set forth in SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, respectively (the CDRs of a light chain variable region of the Ofatumumab antibody), and a heavy chain variable region (V_H) of the anti-CD20 antigen-binding region includes three CDRs that are identical to CDR1, CDR2 and CDR3 as set forth in SEQ ID NO: 127, SEQ ID NO: 128, SEQ ID NO: 129, respectively (the CDRs of a heavy chain variable region of the Ofatumumab antibody).

[0115] A light chain variable region (V_L) of the anti-BCMA antigen-binding region can comprise one, two, or three complementarity determining regions (CDRs), CDR1, CDR2 and CDR3, that are at least or about 70%, at least or about 75%, at least or about 80%, at least or about 85%, at least or about 90%, at least or about 95%, at least or about 99%, at least or about 81%, at least or about 82%, at least or about 83%, at least or about 84%, at least or about 85%, at least or about 86%, at least or about 87%, at least or about 88%, at least or about 89%, at least or about 90%, at least or about 91%, at least or about 92%, at least or about 93%, at least or about 94%, at least or about 95%, at least or about 96%, at least or about 97%, at least or about 98%, at least or about 99%, or about 100%, identical to CDR1, CDR2 and CDR3 as set forth position 24-34, position 50-56, position 89-97 of SEQ ID NO: 12, respectively (the CDRs of a light chain variable region of the BCMA-20 antibody).

[0116] A light chain variable region (V_L) of the anti-BCMA antigen-binding region can comprise one, two, or three complementarity determining regions (CDRs), CDR1, CDR2 and CDR3, that are at least or about 70%, at least or about 75%, at least or about 80%, at least or about 85%, at least or about 90%, at least or about 95%, at least or about 99%, at least or about 81%, at least or about 82%, at least or about 83%, at least or about 84%, at least or about 85%, at least or about 86%, at least or about 87%, at least or about 88%, at least or about 89%, at least or about 90%, at least or about 91%, at least or about 92%, at least or about 93%, at least or about 94%, at least or about 95%, at least or about 96%, at least or about 97%, at least or about 98%, at least or about 99%, or about 100%, identical to CDR1, CDR2 and CDR3 as set forth SEQ ID NO: 134, SEQ ID NO: 136, SEQ ID NO: 138, respectively (the CDRs of a light chain variable region of the BCMA-20 antibody).

[0117] A heavy chain variable region (V_H) of the anti-BCMA antigen-binding region can comprise one, two, or three complementarity determining regions (CDRs), CDR1, CDR2 and CDR3, that are at least or about 70%, at least or about 75%, at least or about 80%, at least or about 85%, at least or about 90%, at least or about 95%, at least or about 99%, at least or about 81%, at least or about 82%, at least or about 83%, at least or about 84%, at least or about 85%, at least or about 86%, at least or about 87%, at least or about 88%, at least or about 89%, at least or about 90%, at least or about 91%, at least or about 92%, at least or about 93%, at least or about 94%, at least or about 95%, at least or about 96%, at least or about 97%, at least or about 98%, at least or about 99%, or about 100%, identical to CDR1, CDR2 and CDR3 as set forth in position 31-35, position 50-66, position 99-111 of SEQ ID NO: 16, respectively (the CDRs of a heavy chain variable region of the BCMA-20 antibody).

96%, at least or about 97%, at least or about 98%, at least or about 99%, or about 100%, identical to CDR1, CDR2 and CDR3 as set forth in position 31-35, position 50-66, position 99-110 of SEQ ID NO: 16, respectively (the CDRs of a heavy chain variable region of the BCMA-20 antibody).

[0118] A heavy chain variable region (V_H) of the anti-BCMA antigen-binding region can comprise one, two, or three complementarity determining regions (CDRs), CDR1, CDR2 and CDR3, that are at least or about 70%, at least or about 75%, at least or about 80%, at least or about 85%, at least or about 90%, at least or about 95%, at least or about 99%, at least or about 81%, at least or about 82%, at least or about 83%, at least or about 84%, at least or about 85%, at least or about 86%, at least or about 87%, at least or about 88%, at least or about 89%, at least or about 90%, at least or about 91%, at least or about 92%, at least or about 93%, at least or about 94%, at least or about 95%, at least or about 96%, at least or about 97%, at least or about 98%, at least or about 99%, or about 100%, identical to CDR1, CDR2 and CDR3 as set forth in SEQ ID NO: 141, SEQ ID NO: 143, SEQ ID NO: 145, respectively (the CDRs of a heavy chain variable region of the BCMA-20 antibody).

[0119] In certain embodiments, a light chain variable region (V_L) of the anti-BCMA antigen-binding region includes three CDRs, CDR1, CDR2 and CDR3, that are identical to CDR1, CDR2 and CDR3 as set forth position 24-34, position 50-56, position 89-97 of SEQ ID NO: 12, respectively (CDRs of a light chain variable region of the BCMA-20 antibody), and a heavy chain variable region (V_H) of the anti-BCMA antigen-binding region includes three CDRs, CDR1, CDR2 and CDR3, that are identical to CDR1, CDR2 and CDR3 as set forth in position 31-35, position 50-66, position 99-110 of SEQ ID NO: 16, respectively (CDRs of a heavy chain variable region of the BCMA-20 antibody).

[0120] In certain embodiments, a light chain variable region of the anti-BCMA antigen-binding region includes three CDRs, CDR1, CDR2 and CDR3, that are identical to CDR1, CDR2 and CDR3 as set forth SEQ ID NO: 134, SEQ ID NO: 136, SEQ ID NO: 138, respectively (CDRs of a light chain variable region (V_L) of the BCMA-20 antibody), and a heavy chain variable region (V_H) of the anti-BCMA antigen-binding region includes three CDRs, CDR1, CDR2 and CDR3, that are identical to CDR1, CDR2 and CDR3 as set forth in SEQ ID NO: 141, SEQ ID NO: 143, SEQ ID NO: 145, respectively (CDRs of a heavy chain variable region of the BCMA-20 antibody).

[0121] In certain embodiments, in the present CAR, the antigen binding domain targeting CD20 comprises a light chain variable domain V_L (SEQ ID NO: 4) and a heavy chain variable domain V_H (SEQ ID NO: 8) derived from the Ofatumumab antibody.

[0122] The light chain variable domain V_L derived from the Ofatumumab (OF) antibody may have the below sequence:

(SEQ ID NO: 4)
EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYD
ASN RATGIPARFSGSGSGTDFLTISLEPEDFAVYYCQQRSNWPITFGQ
 GTRLEIK

[0123] OF-VL-CDR1: SEQ ID NO: 4, position 24-34. The sequence of OF-VL-CDR1 is: RASQSVSSYLA (SEQ ID NO: 130).

[0124] OF-VL-CDR2: SEQ ID NO: 4, position 50-56. The sequence of OF-VL-CDR2 is: DASNRAT (SEQ ID NO: 131).

[0125] OF-VL-CDR3: SEQ ID NO: 4, position 89-97. The sequence of OF-VL-CDR3 is: QQRSNWPIT (SEQ ID NO: 132).

[0126] The heavy chain variable domain V_H derived from the Ofatumumab antibody may have the below sequence:

(SEQ ID NO: 8)
EVQLVESGGGLVQPGRLSRLSCAASGFTFNDYAMHWVRQAPGKGLVWVST
ISWNSGSIGYADSVKGRFTISRDNAKSLYQMNSLRAEDTALYYCAKDI
QYGNYYYYGMDVWQGTTVTVSS

[0127] OF-VH-CDR1: SEQ ID NO: 8, position 30-35. The sequence of OF-VH-CDR1 is: NDYAMH (SEQ ID NO: 127).

[0128] OF-VH-CDR2: SEQ ID NO: 8, position 50-66. The sequence of OF-VH-CDR2 is: TISWNSGSIG-YADSVKG (SEQ ID NO: 128).

[0129] OF-VH-CDR3: SEQ ID NO: 8, position 99-111. The sequence of OF-VH-CDR3 is: DIQYGNYYYYGMDV (SEQ ID NO: 129).

[0130] In certain embodiments, the antigen-binding domain targeting BCMA in the present CAR comprises a light chain variable domain V_L (SEQ ID NO: 12) and a heavy chain variable domain V_H (SEQ ID NO: 16) derived from the BCMA-20 (B20) antibody.

[0131] The light chain variable domain V_L derived from the BCMA-20 antibody may have the below sequence:

(SEQ ID NO: 12)
DIQMTQSPSSLSASVGDRVTITCRASQGISNYLNWYQQKPGKAPKPLIYY
TSNLQSGVPSRSRGSGSGTDYTLTISSLQPEDFATYYCMGQTISSYTFGQ
GTKLEIK

[0132] B20-VL-CDR1: SEQ ID NO: 12, position 24-34. The sequence of B20-VL-CDR1 is: RASQGISNYLN (SEQ ID NO: 134).

[0133] B20-VL-CDR2: SEQ ID NO: 12, position 50-56. The sequence of B20-VL-CDR2 is: YTSNLQS (SEQ ID NO: 136).

[0134] B20-VL-CDR3: SEQ ID NO: 12, position 89-97. The sequence of B20-VL-CDR3 is: MGQTISSYT (SEQ ID NO: 138).

[0135] The heavy chain variable domain V_H derived from the BCMA-20 antibody may have the below sequence:

(SEQ ID NO: 16)
EVQLVESGGGLVQPGGLSRLSCAASGFTFSNFDMAWVRQAPGKGLVWVSS
ITTGADHAIYADSVKGRFTISRDNAKNTLYLQMNSLRAEDTAVYYCVRHG
YYDGYHLFDYWQGTLVTVSS

[0136] B20-VH-CDR1: SEQ ID NO: 16, position 31-35. The sequence of B20-VH-CDR1 is: NFDMA (SEQ ID NO: 141).

[0137] B20-V H-CDR2: SEQ ID NO: 16, position 50-66. The sequence of B20-V H-CDR2 is: SITTGADHAI-YADSVKG (SEQ ID NO: 143).

[0138] B20-VH-CDR3: SEQ ID NO: 16, position 99-110. The sequence of B20-VH-CDR3 is: HGYYDGYHLFDY (SEQ ID NO: 145).

[0139] The signal peptide may be the signal peptide of CD8, having the following sequence: MALPVTALL-PLALLHAARP (SEQ ID NO: 2)

[0140] The linker between V_L and V_H (or V_H and V_L) of the anti-CD20 scFv (linker-1) may have the following sequence: GSTSGGGSGGGSGGGGSS (SEQ ID NO: 6)

[0141] The linker between the anti-CD20 scFv and the anti-BCMA scFv (linker-2) may have the following sequence: GGGGS (SEQ ID NO: 10)

[0142] The linker between V_L and V_H (or V_H and V_L) of the anti-BCMA scFv (linker-3) may have the following sequence: GGGGSGGGGSGGGGS (SEQ ID NO: 14)

[0143] The hinge region between the extracellular region (antigen-binding domain) and the transmembrane domain may be derived from IgG4, CD8 (CD8a), CD28, CD137, or combinations thereof.

[0144] The hinge region may be derived from CD8a which has the following sequence: FVPVFLPAKPTTPAPRPT-PAPTIASQPLSLRPEACRPAAGGAHVTRGLDFACD (SEQ ID NO: 18)

[0145] The hinge region may be derived from IgG4 which has the following sequence:

[0146] ESKYGPCCPPCP (SEQ ID NO: 78)

[0147] The transmembrane domain may be derived from CD8 (CD8TM) which has the following sequence: IYI-WAPLAGTCGVLLSLVITYC (SEQ ID NO: 20)

[0148] The transmembrane domain may be derived from CD28 (CD28TM) which has the following sequence: MFWVLVVVGGLACYSLLVTVAFIIFWV (SEQ ID NO: 80)

[0149] The co-stimulatory region may be derived from 4-1BB which has the following sequence: KRGRKKLLY-IFKQPFMRPVQTTQEEDGCSRFPEEEAGGCEL (SEQ ID NO: 22)

[0150] The cytoplasmic signaling domain may be derived from CD3Q which has the following sequence:

(SEQ ID NO: 24)
RVKFSRSADAPAYQQQNOLYNENLGRREYDVLDKRRGRDPEMGGKPR
RKNPQEGLYNELQDKMAEAYSEIGMKGERRRGKGDGLYQGLSTATKDT
YDALHMQALPPR

Chimeric Antigen Receptors (CARs)

[0151] The terms “chimeric antigen receptor,” or alternatively “CAR”, are used interchangeably throughout and refer to a recombinant polypeptide construct comprising, e.g., an extracellular antigen binding domain, a transmembrane domain and an intracellular domain. Lee et al., *Clin. Cancer Res.* (2012) 18(10):2780; Jensen et al., *Immunol Rev.* (2014) 257(1):127. In one embodiment, the stimulatory molecule is the zeta chain associated with the T cell receptor complex.

[0152] In one aspect, the cytoplasmic signaling domain further comprises one or more functional signaling domains derived from at least one costimulatory molecule. The

costimulatory molecule may also be 4-1BB (i.e., CD137), CD27 and/or CD28 or fragments of those molecules. In another aspect, the CAR comprises a chimeric fusion protein comprising an extracellular antigen recognition domain, a transmembrane domain and an intracellular signaling domain comprising a functional signaling domain derived from a stimulatory molecule. The CAR may comprise a chimeric fusion protein comprising an extracellular antigen recognition domain, a transmembrane domain and an intracellular signaling domain comprising a functional signaling domain derived from a co-stimulatory molecule and a functional signaling domain derived from a stimulatory molecule. Alternatively, the CAR may comprise a chimeric fusion protein comprising an extracellular antigen recognition domain, a transmembrane domain and an intracellular signaling domain comprising two functional signaling domains derived from one or more co-stimulatory molecule(s) and a functional signaling domain derived from a stimulatory molecule. The CAR may also comprise a chimeric fusion protein comprising an extracellular antigen recognition domain, a transmembrane domain and an intracellular signaling domain comprising at least two functional signaling domains derived from one or more co-stimulatory molecule(s) and a functional signaling domain derived from a stimulatory molecule. The antigen-binding region of the CAR may contain any antigen-binding antibody fragment. The antibody fragment can comprise one or more CDRs, the variable region (or portions thereof), the constant region (or portions thereof), or combinations of any of the foregoing.

[0153] The term “zeta” or alternatively “zeta chain”, “CD3-zeta” or “TCR-zeta” may be the protein provided as GenBank accession numbers NP_932170, NP_000725, or XP_011508447; or the equivalent residues from a non-human species, e.g., mouse, rodent, monkey, ape and the like, and a “zeta stimulatory domain” or alternatively a “CD3-zeta stimulatory domain” or a “TCR-zeta stimulatory domain” may be the amino acid residues from the cytoplasmic domain of the zeta chain that are sufficient to functionally transmit an initial signal necessary for T cell activation.

[0154] A chimeric receptor may refer to a non-naturally occurring molecule that can be expressed on the surface of a host cell and comprises an antigen-binding fragment that binds to an antigen. In addition to the antigen-binding fragment, the chimeric receptor may further comprise one or more of a hinge region, a transmembrane domain, at least one co-stimulatory region, and a cytoplasmic signaling domain. In some embodiments, the chimeric antigen receptor comprises from N terminus to C terminus, an antigen-binding region (or fragment), a hinge region, a transmembrane domain, and a cytoplasmic signaling domain. In some embodiments, the chimeric antigen receptor further comprises at least one co-stimulatory region. Thus, the chimeric antigen receptor may comprise from N terminus to C terminus, an antigen-binding region (or fragment), a hinge region, a transmembrane domain, a co-stimulatory region, and a cytoplasmic signaling domain.

[0155] In some embodiments, the chimeric antigen receptors comprise a hinge region, which may be located between the antigen-binding region and a transmembrane domain. The hinge region may contain about 10-200 amino acids, e.g., 15-150 amino acids, 20-100 amino acids, or 30-60 amino acids. In some embodiments, the hinge region may be of about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75,

80, 85, 90, 95, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, or 200 amino acids in length. The hinge region may contain 0-300 amino acids, 2 amino acids to 100 amino acids, 5 amino acids to 80 amino acids, 10 amino acids to 60 amino acids, 10 amino acids to 15 amino acids, 20 amino acids to 80 amino acids, 30 amino acids to 70 amino acids, 40 amino acids to 60 amino acids, 50 amino acids to 60 amino acids, or 30 amino acids to 60 amino acids.

[0156] In some embodiments, the hinge region is a hinge domain of a naturally occurring protein. Hinge domains of any protein known in the art to comprise a hinge domain are compatible for use in the chimeric antigen receptors. In some embodiments, the hinge domain is of CD8 α or CD28 α . In some embodiments, the hinge domain is a portion of the hinge domain of CD8 α , e.g., a fragment containing at least 15 (e.g., 20, 25, 30, 35, or 40) consecutive amino acids of the hinge domain of CD8 α or CD28 α .

[0157] Hinge domains of antibodies, such as an IgG, IgA, IgM, IgE, or IgD antibody, are also compatible for use in the chimeric antigen receptors. In some embodiments, the hinge region is the hinge domain that joins the constant domains CH1 and CH2 of an antibody. In some embodiments, the hinge region is of an antibody and comprises the hinge domain of the antibody and one or more constant regions of the antibody. In some embodiments, the hinge region comprises the hinge domain of an antibody and the CH3 constant region of the antibody. In some embodiments, the hinge region comprises the hinge domain of an antibody and the CH2 and CH3 constant regions of the antibody. In some embodiments, the antibody is an IgG, IgA, IgM, IgE, or IgD antibody. In some embodiments, the antibody is an IgG antibody. In some embodiments, the antibody is an IgG1, IgG2, IgG3, or IgG4 antibody. In some embodiments, the hinge region comprises the hinge region and the CH2 and CH3 constant regions of an IgG4 antibody. In some embodiments, the hinge region comprises the hinge region and the CH3 constant region of an IgG4 antibody.

[0158] The hinge region may be a non-naturally occurring peptide. In some embodiments, the hinge region between the extracellular antigen-binding domain and the transmembrane domain is a peptide linker, such as a (GlyxSer) n (or (GxS) n) linker, wherein x and n, independently can be an integer between 3 and 12, including 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or more.

[0159] Additional peptide linkers that may be used in a hinge region of the chimeric receptors described herein are known in the art. See, e.g., Wriggers et al. *Current Trends in Peptide Science* (2005) 80(6): 736-746 and PCT Publication WO 2012/088461.

[0160] In some embodiments, the chimeric antigen receptors may comprise a transmembrane domain. The transmembrane domain can be in any form known in the art. Transmembrane domains compatible for use in the chimeric antigen receptors may be obtained from a naturally occurring protein. Alternatively, the transmembrane domain may be a synthetic, non-naturally occurring protein segment, e.g., a hydrophobic protein segment that is thermodynamically stable in a cell membrane.

[0161] In some embodiments, the transmembrane domain is that of CD8 α . In some embodiments, the transmembrane domain is that of CD28. In some embodiments, the transmembrane domain is that of ICOS.

[0162] In some embodiments, the chimeric antigen receptors comprise one or more costimulatory regions. A co-

stimulatory region may be at least a portion of a protein that mediates signal transduction within a cell to induce an immune response, such as an effector function. The co-stimulatory region of the chimeric antigen receptor can be from a protein which transduces a signal and modulates responses mediated by immune cells, such as T cells, natural killer (NK) cells, macrophages, neutrophils, or eosinophils.

[0163] In some embodiments, the chimeric antigen receptor comprises one or more than one (at least 2, 3, 4, or more) co-stimulatory region. In some embodiments, the chimeric antigen receptor comprises more than one co-stimulatory region obtained from different proteins. In some embodiments, the chimeric antigen receptor does not comprise a co-stimulatory region.

[0164] Examples of co-stimulatory regions for use in the chimeric antigen receptors can be a domain from co-stimulatory proteins, including, without limitation, CD27, CD28, 4-1BB, OX40, CD30, Cd40, PD-1, ICOS, lymphocyte function-associated antigen-1 (LFA-1), CD2, CD7, LIGHT, NKG2C, B7-H3. In some embodiments, the co-stimulatory region is derived from 4-1BB, CD28, or ICOS. In some embodiments, the co-stimulatory region is derived from CD28 and the chimeric antigen receptor comprises a second co-stimulatory region from 4-1BB or ICOS. In some embodiments, the co-stimulatory region is a fusion domain comprising more than one co-stimulatory region or portions of more than one co-stimulatory region. In some embodiments, the costimulatory region is a fusion of costimulatory regions from CD28 and ICOS.

[0165] In some embodiments, the chimeric antigen receptors comprise a cytoplasmic signaling domain. Any cytoplasmic signaling domain can be used in the chimeric antigen receptors described herein. A cytoplasmic signaling domain may relay a signal, such as interaction of an extracellular ligand-binding domain with its ligand, to stimulate a cellular response, such as inducing an effector function of the cell (e.g., cytotoxicity).

[0166] The chimeric antigen receptors can be prepared by routine methods, such as recombinant technology. Methods for preparing the chimeric antigen receptors may involve generation of a nucleic acid that encodes a polypeptide comprising each of the domains of the chimeric antigen receptors, including the antigen-binding fragment and optionally, the hinge region, the transmembrane domain, at least one co-stimulatory region, and the cytoplasmic signaling domain. In some embodiments, nucleic acids encoding each of the components of the chimeric antigen receptor are joined together using recombinant technology. Sequences of each of the components (e.g., domains) can be joined directly or indirectly (e.g., using a nucleic acid sequence encoding a peptide linker) to form a nucleic acid sequence encoding the chimeric antigen receptor, using methods such as PCR amplification or ligation. Alternatively, the nucleic acid encoding the chimeric antigen receptor may be synthesized. In some embodiments, the nucleic acid is DNA. In other embodiments, the nucleic acid is RNA.

[0167] In one embodiment, the present CAR, from the N-terminus to C-terminus, comprises a signal peptide (also known as leader sequence), an antigen recognition sequence (antigen-binding domain), a hinge region, a transmembrane domain, a co-stimulatory region, and a cytoplasmic signaling domain (e.g., a CD3zeta signaling region (Q chain portion)).

[0168] Bispecificity means that the CAR can specifically bind two different antigens. The bispecific CAR may generate an immune response by binding to one antigen or both antigens.

[0169] As used herein, the terms "CAR-T cell", "CAR-T", "CART", "CART cell" may refer to the T cell that expresses the present CAR targeting both CD20 and BCMA.

Immune Cells Expressing Chimeric Antigen Receptors

[0170] The present disclosure also provides immune cells expressing the present CAR. Recognition of a target cell having the antigen(s) on its cell surface by the antigen-binding fragment of the chimeric antigen receptor may transduce an activation signal to the signaling domain(s) (e.g., co-stimulatory region and/or the cytoplasmic signaling domain) of the chimeric antigen receptor, which may activate an effector function in the immune cell expressing the chimeric antigen receptor.

[0171] The chimeric antigen receptor can be introduced into a suitable immune cell for expression via conventional technology. In some embodiments, the immune cells are T cells, such as primary T cells or T cell lines. Alternatively, the immune cells can be natural killer (NK) cells, such as established NK cell lines (e.g., NK-92 cells). In some embodiments, the immune cells are T cells that express CD8 (CD8⁺) or CD8 and CD4 (CD8⁺/CD4⁺). In some embodiments, the T cells are T cells of an established T cell line, for example, Jurkat cells.

[0172] Primary T cells may be obtained from any source, such as peripheral blood mononuclear cells (PBMCs), bone marrow, tissues such as spleen, lymph node, thymus, or tumor tissue. In some embodiments, the population of immune cells is derived from a human patient having an autoimmune disorder or cancer (e.g., hematopoietic malignancy), such as from the bone marrow or from PBMCs obtained from the patient. In some embodiments, the population of immune cells is derived from a healthy donor. In some embodiments, the immune cells are obtained from the subject to whom the immune cells expressing the chimeric antigen receptors will be subsequently administered. Immune cells that are administered to the same subject from which the cells were obtained are referred to as autologous cells, whereas immune cells that are obtained from a subject who is not the subject to whom the cells will be administered may be referred to as allogeneic cells.

[0173] The type of immune cells desired may be expanded within the population of cells obtained by co-incubating the cells with stimulatory molecules, for example, anti-CD3 and anti-CD28 antibodies may be used for expansion of T cells.

[0174] To construct the immune cells that express the chimeric antigen receptors described herein, vectors for stable or transient expression of the chimeric antigen receptor may be constructed via conventional methods as described herein and introduced into immune cells. For example, nucleic acids encoding the chimeric antigen receptors may be cloned into a suitable vector, such as a viral vector.

[0175] In certain embodiments, immune cells (e.g., T cells) are transduced with lentiviral vectors (LVs) encoding the present CAR. The transduced immune cells (e.g., T cells) can target CD20 and BCMA, synergistically activate the T cells, and induce T cell-mediated immune responses.

[0176] In one embodiment, in the present method, T cells from an autologous patient (or an allogeneic donor) are

isolated, activated and genetically modified to generate CAR-T cells expressing the present CAR, and then administered to the patient. CAR-T cells can replicate in vivo resulting in long-term persistence. In addition, the CAR-mediated immune response may be part of an adoptive immunotherapy approach in which the anti-CD20/BCMA CAR-T cells elicit an immune response against cells expressing CD20 and/or BCMA.

[0177] In certain embodiments, cells are isolated from a mammal (e.g., a human) and genetically modified (i.e., transduced or transfected in vitro) with a vector expressing a CAR disclosed herein. The CAR-modified cells can be administered to a mammalian recipient to provide a therapeutic benefit. The mammalian recipient may be a human. The CAR-modified cell can be autologous with respect to the recipient. Alternatively, the cells can be allogeneic, syngeneic or xenogeneic with respect to the recipient.

[0178] The methods of preparing immune cells expressing the present chimeric antigen receptors may comprise activating and/or expanding the immune cells ex vivo. Activating an immune cell means stimulating an immune cell into an activated state in which the cell may be able to perform effector functions (e.g., cytotoxicity). Methods of activating an immune cell will depend on the type of the immune cell used for expression of the chimeric antigen receptors. Expanding immune cells may involve any method that results in an increase in the number of cells expressing chimeric antigen receptors, for example, allowing the cells to proliferate or stimulating the cells to proliferate. In some embodiments, the cells expressing the chimeric receptors described herein are activated and/or expanded ex vivo prior to administration to a subject.

[0179] The CAR-expressing immune cells may also serve as a vaccine for ex vivo immunization and/or in vivo therapy in a mammal. In addition to using a cell-based vaccine in terms of ex vivo immunization, the present disclosure also provides compositions and methods for in vivo immunization to elicit an immune response directed against an antigen in a patient. Preferably, the mammal is a human. With respect to ex vivo immunization, one or more of the following may occur in vitro prior to administering the cell into a mammal: i) expanding the cells, ii) introducing a nucleic acid encoding a CAR to the cells, and/or iii) cryopreservation of the cells.

Vectors

[0180] The present disclosure provides a nucleic acid encoding the present CAR. The present disclosure also provides vectors comprising the present nucleic acid.

[0181] The vectors include, but are not limited to, a plasmid, a phagemid, a phage derivative, a virus, and a cosmid.

[0182] The vector may be a viral vector. Viruses, which are useful as vectors comprise, but are not limited to, retroviruses, adenoviruses, adeno-associated viruses, herpes viruses, and lentiviruses. In certain embodiments, the present vector is a retroviral vector such as a lentiviral vector. In some embodiments, the vectors for expression of the chimeric antigen receptors are retroviruses. In some embodiments, the vectors for expression of the chimeric antigen receptors are lentiviruses. In some embodiments, the vectors for expression of the chimeric antigen receptors are adeno-associated viruses.

[0183] A variety of promoters can be used for expression of the chimeric receptors, including, without limitation, cytomegalovirus (CMV) intermediate early promoter, a viral LTR such as the Rous sarcoma virus LTR, HIV-LTR, HTLV-1 LTR, Maloney murine leukemia virus (MMLV) LTR, myeloproliferative sarcoma virus (MPSV) LTR, spleen focus-forming virus (SFFV) LTR, the simian virus 40 (SV40) early promoter, herpes simplex tk virus promoter, elongation factor 1-alpha (EF1- α) promoter with or without the EF1- α intron. Additional promoters for expression of the chimeric receptors include any constitutively active promoter in an immune cell. Alternatively, any regulatable promoter (e.g., inducible promoters) may be used, such that its expression can be modulated within an immune cell.

[0184] The vector can be introduced into a cell, e.g., mammalian, bacterial, yeast, or insect cell, by any method in the art. For example, the vector can be transferred into a cell by physical, chemical, or biological means.

[0185] Physical methods for introducing a polynucleotide into a cell comprise calcium phosphate precipitation, lipofection, particle bombardment, microinjection, electroporation, and the like. See, for example, Sambrook et al. (2001, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory, New York).

[0186] Biological methods for introducing a polynucleotide of interest into a cell comprise the use of DNA and RNA vectors. Viral vectors can be derived from retroviruses, lentiviruses, poxviruses, herpes simplex virus I, adenoviruses and adeno-associated viruses, and the like.

[0187] Chemical means for introducing a polynucleotide into a host cell comprise colloidal dispersion systems, such as macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. An exemplary colloidal system for use as a delivery vehicle in vitro and in vivo is a liposome (e.g., an artificial membrane vesicle).

[0188] In some embodiments, the vector (nucleic acid) encoding the chimeric antigen receptor is a DNA vector and may be electroporated to immune cells (see, e.g., Till, et al. Blood (2012) 119(17): 3940-3950). In some embodiments, the vector (nucleic acid) encoding the chimeric antigen receptor is an RNA molecule, which may be electroporated to immune cells.

[0189] Any of the vectors comprising a nucleic acid that encodes a chimeric antigen receptor described herein is also within the scope of the present disclosure. Such a vector may be delivered into host cells such as immune cells by a suitable method. Methods of delivering vectors to immune cells are well known in the art and may include DNA, RNA, or transposon electroporation, transfection reagents such as liposomes or nanoparticles to delivery DNA, RNA, or transposons; delivery of DNA, RNA, or transposons or protein by mechanical deformation (see, e.g., Sharei et al. PNAS (2013) 110(6): 2082-2087); or viral transduction. In some embodiments, the vectors for expression of the chimeric receptors are delivered to cells by viral transduction.

[0190] In examples in which the vectors encoding chimeric antigen receptors are introduced to the host cells using a viral vector, viral particles that are capable of infecting the immune cells and carry the vector may be produced by any method known in the art. The viral particles are harvested

from the cell culture supernatant and may be isolated and/or purified prior to contacting the viral particles with the immune cells.

Pharmaceutical Compositions

[0191] The present disclosure provides a pharmaceutical composition comprising the present immune cells, the present CAR, the present nucleic acid, or the present vector. The present pharmaceutical composition may further comprise a pharmaceutically acceptable carrier, diluent or excipient. In one embodiment, the preparation is a liquid preparation. In one embodiment, the concentration of the immune cells (e.g., CAR-T cells) in the preparation is 1×10^3 - 1×10^8 cells/mL, or 1×10^4 - 1×10^7 cells/mL.

[0192] Effective amounts vary, as recognized by those skilled in the art, depending on the particular condition being treated, the severity of the condition, the individual patient parameters including age, physical condition, size, gender and weight, the duration of the treatment, the nature of concurrent therapy (if any), the specific route of administration and like factors within the knowledge and expertise of the health practitioner. In some embodiments, the effective amount alleviates, relieves, ameliorates, improves, reduces the symptoms, or delays the progression of a disease or disorder in the subject. In some embodiments, the subject is a mammal. In some embodiments, the subject is a human.

[0193] Pharmaceutically acceptable carriers, including buffers, are well known in the art, and may comprise phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives; low molecular weight polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; amino acids; hydrophobic polymers; monosaccharides; disaccharides; and other carbohydrates; metal complexes; and/or non-ionic surfactants. See, e.g. Remington: The Science and Practice of Pharmacy 20th Ed. (2000) Lippincott Williams and Wilkins, Ed. K. E. Hoover.

[0194] The present pharmaceutical composition may be delivered to a cell by contacting the cell with the present pharmaceutical composition.

[0195] The present pharmaceutical composition may be delivered/administered to a subject by any route, including, without limitation, intravenous, intracerebroventricular (ICV) injection, intracisternal injection or infusion, oral, transdermal, ocular, intraperitoneal, subcutaneous, implant, sublingual, subcutaneous, intramuscular, rectal, mucosal, ophthalmic, intrathecal, intra-articular, intra-arterial, subarachnoid, bronchial and lymphatic administration. The present pharmaceutical composition may be administered parenterally or systemically. The present composition may be administered locally. The pharmaceutical composition may be formulated for intravenous administration.

[0196] The administration of the present compositions may be carried out in any convenient manner, including by aerosol inhalation, injection, ingestion, transfusion, implantation or transplantation. The compositions may be administered to a patient subcutaneously, intradermally, intratumorally, intranodally, intramedullary, intramuscularly, by intravenous (i.v.) injection, or intraperitoneally. In one embodiment, the compositions are administered to a subject (e.g., a patient) by intradermal or subcutaneous injection. In another embodiment, the compositions are administered by i.v. injection. The compositions may be injected directly into a tumor, lymph node, or site of disorder.

[0197] The present immune cells or pharmaceutical composition may be delivered/administered to a subject via intravenous, intramuscular, subcutaneous, intraperitoneal, spinal or other parenteral administration, such as by injection or infusion.

[0198] The present pharmaceutical compositions may be administered in a manner appropriate to the disease to be treated (or prevented). The quantity and frequency of administration will be determined by such factors as the condition of the patient, and the type and severity of the patient's disease, although appropriate dosages may be determined by clinical trials.

[0199] When "an effective amount", "a therapeutically effective amount", or "a therapeutic amount" is indicated, the precise amount of the compositions to be administered can be determined by a physician with consideration of individual differences in age, weight, tumor size, extent of infection or metastasis, and condition of the patient (subject). A pharmaceutical composition comprising the immune cells may be administered at a dosage of 10^4 to 10^9 cells/kg body weight, or 10^5 to 10^6 cells/kg body weight, including all integer values within those ranges. The compositions may also be administered multiple times at these dosages. The cells can be administered by using infusion techniques that are commonly known in immunotherapy (see, e.g., Rosenberg et al, New Eng. J. of Med. 319: 1676, 1988). The optimal dosage and treatment regime for a particular patient can readily be determined by one skilled in the art of medicine by monitoring the patient for signs of disease and adjusting the treatment accordingly.

[0200] The dosage of the above treatments to be administered to a patient may vary with the precise nature of the condition being treated and the recipient of the treatment. The scaling of dosages for patient administration can be performed according to art-accepted practices. In one embodiment, 1×10^6 to 1×10^{10} of the immune cells (e.g., CAR-T cells) can be administered to a patient by means of, for example, intravenous infusion for each treatment or each course of treatment.

Conditions to be Treated

[0201] The present CAR, immune cells or pharmaceutical composition may be used to treat an autoimmune disease/disorder, or to treat cancer or tumor.

[0202] In certain embodiments, the present anti-CD20/BCMA bispecific CAR targets both B cells and plasma cells, which may reduce/eradicate autoimmune antibodies. In certain embodiments, the present anti-CD20/BCMA bispecific CAR may reduce/deplete B cells, plasmablasts, and/or long-lived plasma cells (LL PCs) to reduce/eradicate autoantibody production.

[0203] The present disclosure provides for a method of treating an autoimmune disease/disorder. The method may comprise administering the CAR, immune cells or pharmaceutical composition to a subject in need thereof.

[0204] The autoimmune disorder may be systemic lupus erythematosus (SLE), lupus nephritis (LN), systemic sclerosis (SSc), CREST syndrome (calcinosis, Raynaud's syndrome, esophageal dysmotility, sclerodactyl, and telangiectasia), opsoclonus, inflammatory myopathy (e.g., polymyositis, dermatomyositis, and inclusion-body myositis), myositis autoantibody-driven diseases, systemic scleroderma, primary biliary cirrhosis, celiac disease (e.g., gluten sensitive enteropathy), dermatitis herpetiformis, Miller-

Fisher Syndrome, acute motor axonal neuropathy (AMAN), multifocal motor neuropathy with conduction block, autoimmune hepatitis, antiphospholipid syndrome, Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome, rheumatoid arthritis, chronic autoimmune hepatitis, scleromyositis, myasthenia gravis (MG), Lambert-Eaton myasthenic syndrome, Hashimoto's thyroiditis, Graves' disease, Paraneoplastic cerebellar degeneration, Stiff person syndrome, limbic encephalitis, Isaacs Syndrome, Sydenham's chorea, pediatric autoimmune neuropsychiatric disease associated with *Streptococcus* (PANDAS), encephalitis, diabetes mellitus type 1, neuromyelitis optica (NMO), chronic inflammatory bowel disease, Hashimoto's disease, organ transplant rejection, and/or neuromyelitis optica spectrum disorder (NMOSD).

[0205] The autoimmune disorder may be pernicious anemia, Addison's disease, psoriasis, inflammatory bowel disease (IBD), psoriatic arthritis, Sjögren's syndrome, lupus erythematosus (e.g., discoid lupus erythematosus, drug-induced lupus erythematosus, and neonatal lupus erythematosus), multiple sclerosis, and/or reactive arthritis.

[0206] The autoimmune disorder may be polymyositis, dermatomyositis, multiple endocrine failure, Schmidt's syndrome, autoimmune uveitis, adrenalitis, thyroiditis, autoimmune thyroid disease, gastric atrophy, chronic hepatitis, lupoid hepatitis, atherosclerosis, presenile dementia, demyelinating diseases, subacute cutaneous lupus erythematosus, hypoparathyroidism, Dressler's syndrome, autoimmune thrombocytopenia, idiopathic thrombocytopenic purpura, hemolytic anemia, pemphigus vulgaris, pemphigus, alopecia areata, pemphigoid, scleroderma, progressive systemic sclerosis, adult onset diabetes mellitus (e.g., type II diabetes), male and female autoimmune infertility, ankylosing spondylitis, ulcerative colitis, Crohn's disease, sprue, mixed connective tissue disease, polyarteritis nodosa, systemic necrotizing vasculitis, juvenile onset rheumatoid arthritis, glomerulonephritis, atopic dermatitis, atopic rhinitis, Goodpasture's syndrome, Chagas' disease, sarcoidosis, rheumatic fever, asthma, recurrent abortion, anti-phospholipid syndrome, farmer's lung, erythema multiforme, post cardiotomy syndrome, Cushing's syndrome, autoimmune chronic active hepatitis, bird-fancier's lung, allergic disease, allergic encephalomyelitis, toxic epidermal necrolysis, alopecia, Alport's syndrome, alveolitis, allergic alveolitis, fibrosing alveolitis, interstitial lung disease, erythema nodosum, pyoderma gangrenosum, transfusion reaction, leprosy, malaria, leishmaniasis, trypanosomiasis, Takayasu's arteritis, polymyalgia rheumatica, temporal arteritis, schistosomiasis, giant cell arteritis, ascariasis, aspergillosis, Sampter's syndrome, eczema, lymphomatoid granulomatosis, Behcet's disease, Caplan's syndrome, Kawasaki's disease, dengue, endocarditis, endomyocardial fibrosis, endophthalmitis, erythema elevatum et diutinum, erythroblastosis fetalis, eosinophilic fasciitis, Shulman's syndrome, Felty's syndrome, filariasis, cyclitis, chronic cyclitis, heterochronic cyclitis, Fuch's cyclitis, IgA nephropathy, Henoch-Schönlein purpura, graft versus host disease, transplantation rejection, human immunodeficiency virus infection, echovirus infection, cardiomyopathy, Alzheimer's disease, parvovirus infection, rubella virus infection, post vaccination syndromes, congenital rubella infection, Hodgkin's and non-Hodgkin's lymphoma, renal cell carcinoma, multiple myeloma, Eaton-Lambert syndrome, relapsing polychondritis, malignant melanoma, cryoglobulinemia, Waldenstrom's

macroglobulemia, Epstein-Barr virus infection, mumps, Evan's syndrome, and/or autoimmune gonadal failure.

[0207] The autoimmune diseases also include, e.g., acute disseminated encephalomyelitis, alopecia areata, antiphospholipid syndrome, autoimmune hepatitis, autoimmune myocarditis, autoimmune pancreatitis, autoimmune polyendocrine syndromes autoimmune uveitis, inflammatory bowel disease (Crohn's disease, ulcerative colitis), type I diabetes mellitus (e.g., juvenile onset diabetes), multiple sclerosis, scleroderma, ankylosing spondylitis, sarcoid, pemphigus vulgaris, pemphigoid, psoriasis, myasthenia gravis, systemic lupus erythematosus, rheumatoid arthritis, juvenile arthritis, psoriatic arthritis, Behcet's syndrome, Reiter's disease, Berger's disease, dermatomyositis, polymyositis, antineutrophil cytoplasmic antibody-associated vasculitides (e.g., granulomatosis with polyangiitis (also known as Wegener's granulomatosis), microscopic polyangiitis, and Churg-Strauss syndrome), scleroderma, Sjogren's syndrome, anti-glomerular basement membrane disease (including Goodpasture's syndrome), dilated cardiomyopathy, primary biliary cirrhosis, thyroiditis (e.g., Hashimoto's thyroiditis, Graves' disease), transverse myelitis, allergies, arthritis, fibromyalgia, fibromyotonia, lupus, vitiligo, and Guillane-Barre syndrome.

[0208] The autoimmune diseases include inflammatory bowel disease (IBD), ulcerative colitis, Crohn's disease, sprue, autoimmune arthritis, rheumatoid arthritis, Type I diabetes, multiple sclerosis, graft vs. host disease following bone marrow transplantation, osteoarthritis, juvenile chronic arthritis, Lyme arthritis, psoriatic arthritis, reactive arthritis, spondyloarthropathy, systemic lupus erythematosus, insulin dependent diabetes mellitus, thyroiditis, asthma, psoriasis, dermatitis scleroderma, atopic dermatitis, graft versus host disease, acute or chronic immune disease associated with organ transplantation, sarcoidosis, atherosclerosis, disseminated intravascular coagulation, Kawasaki's disease, Grave's disease, nephrotic syndrome, chronic fatigue syndrome, Wegener's granulomatosis, Henoch-Schoenlein purpura, microscopic vasculitis of the kidneys, chronic active hepatitis, uveitis, septic shock, toxic shock syndrome, sepsis syndrome, cachexia, acquired immunodeficiency syndrome, acute transverse myelitis, Huntington's chorea, Parkinson's disease, Alzheimer's disease, stroke, primary biliary cirrhosis, hemolytic anemia, polyglandular deficiency type I syndrome and polyglandular deficiency type II syndrome, Schmidt's syndrome, adult (acute) respiratory distress syndrome, alopecia, alopecia areata, seronegative arthropathy, arthropathy, Reiter's disease, psoriatic arthropathy, *chlamydia*, *yersinia* and *salmonella* associated arthropathy spondyloarthritis, atheromatous disease/arteriosclerosis, atopic allergy, food allergies, autoimmune bullous disease, *pemphigus vulgaris*, *pemphigus foliaceus*, pemphigoid, linear IgA disease, autoimmune haemolytic anaemia, Coombs positive haemolytic anaemia, acquired pernicious anaemia, juvenile pernicious anaemia, myalgic encephalitis/Royal Free Disease, chronic mucocutaneous candidiasis, giant cell arteritis, primary sclerosing hepatitis, cryptogenic autoimmune hepatitis, Acquired Immunodeficiency Disease Syndrome, Acquired Immunodeficiency Related Diseases, Hepatitis C, common varied immunodeficiency (common variable hypogammaglobulinemia), dilated cardiomyopathy, fibrotic lung disease, cryptogenic fibrosing alveolitis, postinflammatory interstitial lung disease, interstitial pneumonitis, connective tissue disease associated interstitial lung

disease, mixed connective tissue disease associated lung disease, systemic sclerosis associated interstitial lung disease, rheumatoid arthritis associated interstitial lung disease, systemic lupus erythematosus associated lung disease, dermatomyositis/polymyositis associated lung disease, Sjogren's disease associated lung disease, ankylosing spondylitis associated lung disease, vasculitic diffuse lung disease, haemosiderosis associated lung disease, drug-induced interstitial lung disease, radiation fibrosis, bronchiolitis obliterans, chronic eosinophilic pneumonia, lymphocytic infiltrative lung disease, postinfectious interstitial lung disease, gouty arthritis, autoimmune hepatitis, type-1 autoimmune hepatitis (classical autoimmune or lupoid hepatitis), type-2 autoimmune hepatitis (anti-LKM antibody hepatitis), autoimmune mediated hypoglycemia, type B insulin resistance with acanthosis *nigricans*, hypoparathyroidism, acute immune disease associated with organ transplantation, chronic immune disease associated with organ transplantation, osteoarthritis, primary sclerosing cholangitis, idiopathic leucopenia, autoimmune neutropenia, renal disease NOS, glomerulonephritides, microscopic vasulitis of the kidneys, discoid lupus, erythematosus, male infertility idiopathic or NOS, sperm autoimmunity, multiple sclerosis (all subtypes), insulindependent diabetes mellitus, sympathetic ophthalmia, pulmonary hypertension secondary to connective tissue disease, Goodpasture's syndrome, pulmonary manifestation of polyarteritis nodosa, acute rheumatic fever, rheumatoid spondylitis, Still's disease, systemic sclerosis, Takayasu's disease/arteritis, autoimmune thrombocytopenia, idiopathic thrombocytopenia, autoimmune thyroid disease, hyperthyroidism, goitrous autoimmune hypothyroidism (Hashimoto's disease), atrophic autoimmune hypothyroidism, primary myxoedema, phacogenic uveitis, primary vasculitis, vitiligo, allergic rhinitis (pollen allergies), anaphylaxis, pet allergies, latex allergies, drug allergies, allergic rhinoconjunctivitis, eosinophilic esophagitis, hypereosinophilic syndrome, eosinophilic gastroenteritis cutaneous lupus erythematosus, eosinophilic esophagitis, hypereosinophilic syndrome, and eosinophilic gastroenteritis.

[0209] The autoimmune disorder may be an inflammatory muscle disease. Inflammatory myopathies are a group of diseases that involve chronic muscle inflammation, muscle weakness, and in some cases, muscle pain. The four main types of chronic, or long-term, inflammatory myopathy are: polymyositis, which affects skeletal muscles (the type involved in body movement) on both sides of the body; dermatomyositis, which causes progressive muscle weakness; inclusion body myositis, which is characterized by slow, progressive muscle weakness and muscle shrinking and loss of muscle; and necrotizing autoimmune myopathy, which involves muscle weakness in the upper and lower body.

[0210] In another embodiment, the autoimmune disease is an autoimmune disease caused by overexpression of B cells (such as lupus erythematosus).

[0211] Also encompassed by the present disclosure is a method of treating cancer. The method may comprise administering the CAR, immune cells or pharmaceutical composition to a subject in need thereof.

[0212] The present disclosure provides chimeric antigen receptors for treating CD20-positive diseases such as B cell lymphoma.

[0213] The cancer may be a BCMA-positive malignancy. The cancer may be multiple myeloma (MM), or plasma cell leukemia.

[0214] The cancer may be a hematologic cancer. The cancer may be a plasma-cell malignancy. The cancer may be a B-cell malignancy. The B-cell malignancy may be acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), B-cell acute lymphoblastic leukemia (B-ALL), B-cell leukemia, or B cell lymphoma.

[0215] The cancer may be Hodgkin's lymphoma, non-Hodgkin's lymphoma, leukemia, and/or multiple myeloma (MM).

[0216] The cancer may be acute myeloid leukemia (AML), multiple myeloma (MM), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia, acute lymphoblastic leukemia (ALL), diffuse large B cell lymphoma (DLBCL), or a combination thereof.

[0217] Diseases that may be treated using the present CAR, immune cells or pharmaceutical composition include CD20-positive tumors and diseases, e.g., caused by excessive B cells (such as autoimmune diseases, for example, lupus erythematosus, etc.). CD20-positive tumors may include CD20-positive non-solid tumors (such as hematological cancer, for example, leukemias and lymphomas) or solid tumors. Tumors or cancers to be treated with present CAR, immune cells or pharmaceutical composition include, but are not limited to, carcinoma, blastoma, and sarcoma, and leukemia or lymphoid malignancies, benign and malignant tumors, and malignancies e.g., sarcomas, carcinomas, gastric cancer, peritoneal metastasis of gastric cancer, liver cancer, renal cancer, lung cancer, small intestine cancer, bone cancer, prostate cancer, colorectal cancer, breast cancer, large intestine cancer, cervical cancer, ovarian cancer, lymphoma, nasopharyngeal carcinoma, adrenal tumor, bladder tumor, non-small cell lung cancer (NSCLC), glioma, endometrial cancer, and melanomas. Adult tumors/cancers and pediatric tumors/cancers are included.

[0218] Hematologic cancers are cancers of the blood or bone marrow. Examples of hematological (or hematogenous) cancers include leukemias, e.g., acute leukemias (such as acute lymphocytic leukemia, acute myelocytic leukemia, acute myelogenous leukemia and myeloblasts, promyelocytic, myelomonocytic, monocytic and erythro-leukemia), chronic leukemias (such as chronic myelocytic (granulocytic) leukemia, chronic myelogenous leukemia, and chronic lymphocytic leukemia), polycythemia vera, lymphoma, Hodgkin's disease, non-Hodgkin's lymphoma (indolent and high grade forms), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, myelodysplastic syndrome, hairy cell leukemia and myelodysplasia.

[0219] The cancer may be a solid tumor. Solid tumors can be benign or malignant. Different types of solid tumors are named for the type of cells that form them (such as sarcomas, carcinomas, and lymphomas). Examples of solid tumors, such as sarcomas and carcinomas, include fibrosarcoma, myxosarcoma, liposarcoma, mesothelioma, malignant lymphoma, pancreatic cancer and ovarian cancer.

Kits

[0220] Also within the scope of the present disclosure are kits for use of the present CARs, immune cells, nucleic acids, vectors or pharmaceutical compositions. Such kits

may include one or more containers comprising the present CARs, immune cells, nucleic acids, vectors or pharmaceutical compositions.

[0221] In some embodiments, the kit can comprise instructions for use in any of the methods described herein. The included instructions can comprise a description of administration of the pharmaceutical composition to a subject to achieve the intended activity in a subject. The kit may further comprise a description of selecting a subject suitable for treatment based on identifying whether the subject is in need of the treatment. In some embodiments, the instructions comprise a description of administering the pharmaceutical compositions to a subject who is in need of the treatment.

[0222] The instructions relating to the use of the pharmaceutical compositions generally include information as to dosage, dosing schedule, and route of administration for the intended treatment. The containers may be unit doses, bulk packages (e.g., multi-dose packages) or sub-unit doses.

[0223] The kits provided herein are in suitable packaging. Suitable packaging includes, but is not limited to, vials, bottles, jars, flexible packaging, and the like.

[0224] The following examples of specific aspects for carrying out the present disclosure are offered for illustrative purposes only, and are not intended to limit the scope of the present disclosure in any way.

Example 1 Construction of Anti-CD20/BCMA CARs

[0225] We prepared eight bispecific CARs having the anti-CD20 scFv and anti-BCMA scFv in the same order (i.e., anti-CD20 scFv ("OF") followed by anti-BCMA scFv ("B20")), but with different V_H/V_L orders and having different hinge regions and/or transmembrane domains: TOB1-4 and TOBL1-4, where TOBL1 is C-CAR168 (FIG. 1).

[0226] The anti-CD20/BCMA CAR-T cells were prepared using apheresis from healthy donors. Specifically, PBMCs were isolated from the venous blood of healthy donors by density gradient centrifugation. On day 0, PBMCs were activated in a cell culture flask previously coated with CD3 monoclonal antibody (OKT3) and Retronectin (TAKARA). The medium was GT-551 cell culture medium containing 1% human albumin and 300 U/mL recombinant human interleukin 2 (IL-2). On day 3, activated PBMCs were transduced with lentiviral vectors encoding the anti-CD20/BCMA CARs.

[0227] FIG. 2 shows the expression levels of the anti-CD20 and anti-BCMA CARs on the surface of the T cells. The expression levels of anti-BCMA CARs were detected by flow cytometry using BCMA-Fc fusion protein; the expression levels of anti-CD20 CARs were detected by flow cytometry using antibody specific to OF scFv.

Example 2 Antigen-Specific Activation of Anti-CD20/BCMA CAR-T Cells In Vitro

[0228] Antigen-specific activation of the anti-CD20/BCMA CAR-T was evaluated by assaying IFN- γ release and CD137 expression when the CAR-T cells were co-cultured with target cells. Target cells ("T") included CD20-positive A549-CD20+ tumor cells, BCMA-positive A549-BCMA+ tumor cells, CD20 and BCMA double positive A549-CD20+BCMA+ tumor cells, Raji cells, MM.1S cells, and double

negative A549 tumor cells. Effector cells ("E") are the anti-CD20/BCMA CAR-T cells.

[0229] PBMCs were isolated from the venous blood of healthy donors by density gradient centrifugation. On day 0, PBMCs were activated in a cell culture flask previously coated with CD3 monoclonal antibody (OKT3) and Retronectin (TAKARA). The medium was GT-551 cell culture medium containing 1% human albumin and 300 U/mL recombinant human interleukin 2 (IL-2). On day 3, activated PBMCs were transduced with lentiviral vectors encoding the anti-CD20/BCMA CARs. Starting from day 6, the CAR-T cells can be taken for activity assays.

[0230] IFN- γ release was assayed using the CAR-T cells cultured for 7 days. 1×10^5 of CAR-T cells were cultured with CD20-positive A549-CD20+ tumor cells, BCMA-positive A549-BCMA+ tumor cells, CD20 and BCMA double positive A549-CD20+BCMA+ tumor cells, double negative A549 tumor cells, or without tumor cells (NT), in 200 μ l of medium for 18 h with an E:T ratio of 1:1. Then the levels of IFN- γ secreted in the cell culture supernatant were detected by ELISA.

[0231] Expression levels of CD137 were assayed using the CAR-T cells cultured for 7 days. 1×10^5 of CAR-T cells were cultured with CD20-positive A549-CD20+ tumor cells, BCMA-positive A549-BCMA+ tumor cells, CD20 and BCMA double positive A549-CD20+BCMA+ tumor cells, double negative A549 tumor cells, or without tumor cells, in 200 μ l of medium for 18 h with an E:T ratio of 1:1. Then the expression levels of CD137 on the surface of the CAR-T cells were detected by flow cytometry.

[0232] The IFN- γ release results are shown in FIGS. 3A-3C and FIG. 6B. After co-culturing the CAR-T cells with A549 cells expressing CD20 and/or BCMA antigens, anti-CD20 CAR-T (C-CAR066) cells can specifically recognize CD20 single-positive or CD20/BCMA double-positive target cells and release IFN- γ . Similarly, anti-BCMA CAR-T (C-CAR088) cells can specifically recognize BCMA single-positive or CD20/BCMA double-positive target cells to release IFN- γ . Only anti-CD20/BCMA CAR-T (TOB1-4 and TOBL1-4, where TOBL1 is C-CAR168) cells can recognize CD20 single-positive, BCMA single-positive and CD20/BCMA double-positive target cells, as well as release high levels of IFN- γ . TOB1 to TOB4 CAR-T cells showed high IFN- γ release when co-cultured with CD20 positive targets, but lower reactivity to BCMA single positive target cells. TOBL1 to TOBL4 CAR-T cells showed high IFN- γ release when co-cultured with CD20 positive targets and BCMA positive target cells. TOBL1 to TOBL4 CAR-T cells showed high IFN- γ release when co-cultured with target cells naturally expressing CD20 and BCMA.

[0233] The flow cytometry results showed that the anti-CD20/BCMA CAR-T cells were activated by a variety of CD20/BCMA single-positive or double-positive cells and up-regulated the expression level of CD137 (FIGS. 4A and 4B).

Example 3 Cytotoxicity of Anti-CD20/BCMA CAR-T Cells In Vitro

[0234] The anti-CD20/BCMA CAR-T cells were co-cultured with target cells at E:T ratios of 0:1, 0.25:1, 0.5:1, 1:1, 2:1 and 4:1, respectively. Real-Time Cell Analysis (RTCA) label-free technology was used to evaluate the cytotoxicity of the CAR-T cells on target cells.

[0235] The results show that the anti-CD20/BCMA CAR-T cells effectively killed CD20/BCMA single-positive or double-positive tumor cells in vitro (A549-CD20+, A549-BCMA+, A549-BCMA+CD20+), while they had no effect on A549 cells which do not express CD20 or BCMA (FIGS. 5A-5B, FIG. 6C). Their killing ability was comparable to the anti-CD20 and anti-BCMA monospecific CAR-T cells, with all being dose-dependent (FIGS. 5A-5B, FIG. 6C). The TOBL1 to TOBL4 CAR-T cells (FIG. 5B) showed high cytotoxicity to CD20-positive and BCMA-positive target cells. The TOB1 to TOB4 CAR-T cells (FIG. 5A) showed lower cytotoxicity to BCMA single positive target cells (compared to anti-BCMA CAR which is C-CAR088).

Example 4 Cytotoxicity of Anti-CD20/BCMA CAR-T Cells on Autoreactive B Cells In Vitro

[0236] Recent studies have shown that in patients with systemic lupus erythematosus (SLE), the proportion of CD11c^{hi}T-bet⁺ B cell subsets is significantly increased, and is closely related to the production of autoantibodies and the patient's clinical manifestations. Autoantibodies are characteristics of reactive B cells (see, Distinct Effector B Cells Induced by Unregulated Toll-like Receptor 7 Contribute to Pathogenic Responses in Systemic Lupus Erythematosus, *Immunity*, 2018, 16; 49(4):725-739.e6. IL-21 drives expansion and plasma cell differentiation of autoreactive CD11chiT-bet⁺ B cells in SLE, *Nat. Commun.* 2018; 9(1): 1758). This subset of cells is enriched with age in some animal models of autoimmune diseases and in the peripheral blood of patients with rheumatoid arthritis, so they are also called age-associated B cells (ABCs) (see, Toll-like receptor 7 (TLR7)-driven accumulation of a novel CD11c⁺ B-cell population is important for the development of autoimmunity. *Blood*, 2011; 118(5):1305-15. A B-cell subset uniquely responsive to innate stimuli accumulates in aged mice, *Blood*, 2011; 118(5):1294-304).

[0237] TLR7 activation plays a role in the accumulation of autoreactive B cells and the production of autoantibodies in autoimmune diseases. One of the consequences of aberrant TLR7 activation is the accumulation of autoreactive B cells, or age-associated B cells (ABCs). ABCs are B cells that recognize self-antigens and have the potential to produce autoantibodies, which can target and damage the body's own tissues. Wang et al., *Nature Communications*, (2018) 9:1758.

[0238] In order to verify that the anti-CD20/BCMA CAR-T cells also have the ability to eliminate ABCs, we prepared C-CAR168 (TOBL1) CAR-T cells from the peripheral blood of three healthy human donors (HD10, HD11 and HD12). We also isolated autologous B cells from the PBMCs of healthy donors and induced their differentiation in vitro to obtain ABC-enriched autologous B cells which were then used as target cells to perform cytotoxicity experiments. After co-culture for 2 to 4 hours, C-CAR168 CAR-T cells derived from different donors showed apparent cytotoxicity effects on the ABC-enriched autologous B cells at different E:T ratios compared with control T cells without CAR transduction (FIGS. 7A-7C).

[0239] C-CAR168 can target both CD20+B cells and BCMA+plasma cells, which can provide superior duration of response in autoimmune diseases. The results show C-CAR168 CAR-T cells can eliminate ABC cells efficiently.

In Vitro ABC Differentiation

[0240] PBMCs from healthy donors were isolated by gradient centrifugation using Ficoll and cryopreserved. On the day of ABC differentiation, pan B cells were first isolated from thawed PBM C by human B cell isolation kit (Miltenyi Biotec; negative selection, e.g., non-B cells were labeled and depleted) according to the manufacturer's instructions. B cells were then seeded in 96-well plates with 200 µl RPMI complete medium and stimulated with TLR7 ligand R848, CD40L, BAFF, IL-2, Goat Anti-Human IgA+IgG+IgM (H+L), IL-21, and IFN-γ for 3 days. Cell medium was exchanged every day by replenishing with the complete medium and stimulation cocktail. The induction of ABCs was confirmed by FACS analysis. Antibodies for FACS staining included live/dead dye, anti-human CD19, CD38, CD27, IgD, CD11c, CD21, and T-bet.

Cytotoxicity Assay

[0241] After differentiation, the ABC-enriched B cells were cocultured with C-CAR168 or non-transduced (NT) T cells at the indicated E:T ratios. After 24 hours, cells were stained with the LIVE/DEAD Fixable Aqua Dead Cell Stain (Invitrogen) to determine their viability, along with anti-CD19 and anti-CD3 antibodies to distinguish B and T cells. Cytotoxicity was determined by the depletion of the percentage of viable CD19⁺ cells. The cytolysis of B cells was calculated by the following formula: Percentage of lysis (%)=(1-(viable CD19⁺ cell fraction of the C-CAR168 coculture/viable CD19⁺ cell fraction of UT coculture))×100. See, Lin et al., Preclinical evaluation of CD8+ anti-BCMA mRNA CART-cells for treatment of multiple myeloma. *Leukemia*. 2021, 35(3): 752-763.

Example 5 Inhibitory Effect of Anti-CD20/BCMA CAR-T Cells on Tumor Cells in Mice

C-CAR168 Effectively Inhibited the Growth of CD20 Single Positive and BCMA Single Positive Tumor Cells in Tumor-Bearing Mice

[0242] The in vivo cytotoxicity effect of the anti-CD20/BCMA CAR-T cells on CD20 or BCMA single-positive cells was evaluated by mouse subcutaneous tumor model established using tumor cell lines expressing either CD20 (A549-CD20) or BCMA (MM.1S).

[0243] 6-8 weeks female B-NDG mice were subcutaneously inoculated with A549-CD20 (CD20+) or MM.1S (BCMA+) cells. When the average tumor volume reached 100 mm³, C-CAR168 CAR-T cells were administered via the tail vein at the dosage of 3-5×10⁶ CAR-T cells/mouse. During the experiment, the tumor volume of the mice treated with the C-CAR168 CAR-T cells continued to decrease. At the end of the experiment, the tumor weight of the C-CAR168 groups was significantly lower than that of the vehicle control group. C-CAR168 cells showed strong cytotoxicity towards CD20-positive and BCMA-positive target cells in vivo.

[0244] Specifically, female B-NDG (NOD.Cg-Prkdc^{scid} II2rg^{tm1Vst}/Vst) mice were subcutaneously inoculated with 5×10⁶ A549-CD20 cells/animal. When the average tumor volume reached about 100 mm³, 20 animals were selected and randomly divided into 2 groups (vehicle control group vs. C-CAR168 group), with 10 animals in each group. A single dose of a vehicle control or C-CAR168 (3×10⁶

CAR-T cells/animal) was administered to the mice by tail vein injection. After administration, the average tumor volume in the vehicle control group continued to increase, reaching 494.16 ± 31.5 mm³ on Day 42, with an average tumor weight of 0.254 ± 0.025 g. The average tumor volumes in the C-CAR168 group began to decrease from Day 10. By Day 42, the average tumor volumes were 10.02 ± 7.04 mm³ (FIG. 9A, left panel), and the tumor weights were 0.013 ± 0.01 g, with significant differences compared to the vehicle control group ($P < 0.001$) (FIG. 9A, right panel). The tumor growth inhibition rates calculated based on tumor weight were 94.88%. The results show that C-CAR168 can significantly inhibit the growth of CD20-positive target cells *in vivo*.

[0245] To evaluate the *in vivo* effects of C-CAR168 on BCMA single positive target cells and compare *in vivo* efficacy of different batches of C-CAR168, 20 female B-NDG (NOD.CB17-Prkdc^{scid}Il2rg^{tm1}/Bcgen) mice were subcutaneously inoculated with 5×10^6 MM.1S cells/animal. When the average tumor volume reached about 100 mm³, 15 animals were selected and randomly divided into 3 groups (a vehicle control group vs. two C-CAR168 groups), with 5 animals in each group. Each mouse was dosed once by tail vein injection. For C-CAR168, the dosage was 5×10^6 CAR-T cells/animal. After administration, the average tumor volume in the vehicle control group continued to increase, reaching 2220.86 ± 117.35 mm³ on Day 28, with a tumor weight of $2,409 \pm 0.216$ g. The average tumor volumes in the C-CAR168-1 and C-CAR168-2 groups began to decrease from Day 10 (FIG. 9B, left panel). By Day 28, the average tumor volumes were 109.2 ± 88.92 mm³ and 9.07 ± 5.58 mm³, respectively, and the tumor weights were 0.041 ± 0.034 g and 0.003 ± 0.002 g, respectively (FIG. 9B, right panel), with significant differences compared to the vehicle control group, ($P < 0.001$, $P < 0.001$). The tumor growth inhibition rates calculated based on tumor weight were 98.30% and 99.88%, respectively. There was no significant difference between the two batches of C-CAR168. The results show that a single intravenous administration of 5×10^6 C-CAR168 CAR-T cells/mouse was well tolerated in B-NDG tumor-bearing mice, and C-CAR168 can significantly inhibit the growth of BCMA-positive target cells *in vivo*.

C-CAR168 Effectively Inhibited the Growth of CD20 and BCMA Double Positive Tumor Cells in Tumor-Bearing Mice

[0246] To evaluate the *in vivo* anti-tumor effects of C-CAR168, 65 female B-NDG (NOD.CB17-Prkdc^{scid}Il2rg^{tm1}/Bcgen) mice were subcutaneous inoculated with 1×10^6 K562-CD20-BCMA cells/animal. When the average tumor volume reached about 100 mm³, 50 animals were selected and randomly divided into 5 groups: vehicle control group, T cell control group, C-CAR168 low-dose group (1×10^6 CAR-T cells/mouse), medium-dose group (5×10^6 CAR-T cells/mouse) and high-dose group (10×10^6 CAR-T cells/mouse). The T cell control group were injected with non-transduced T cells from the same donor as C-CAR168, and the dose was consistent with the total T cell number in the C-CAR168 high-dose group. Each mouse was dosed once by tail vein injection.

[0247] During the experiment, the mean tumor volume of the animals in the vehicle control group and T cell control group continued to increase, and the mean tumor volume

was 2628.78 ± 117.32 mm³ and 2536.23 ± 97.80 mm³, respectively at Day 17. The tumor volume in the C-CAR168 low-dose group continued to increase, although after 10 days of administration, the tumor volume was significantly lower than that in the vehicle control group and T cell control group. The average tumor volume of the C-CAR168 medium-dose group and high-dose group began to decline on Day 6. The C-CAR168 low-dose, medium-dose, and high-dose groups showed dose-dependent reductions in tumor, with tumor growth inhibition rates being 55.47%, 97.75%, and 98.01%, respectively on Day 17. No tumor tissues were observed in the C-CAR168 medium-dose and high-dose groups on Day 28 (FIG. 9E). FIG. 9F shows the survival rate curve of each group during the experimental period. Although all animals in the vehicle control group and T cell control group were dead around Day 17, all mice in the C-CAR168 medium-dose and high-dose groups were alive.

[0248] In summary, a single intravenous administration of 1×10^6 , 5×10^6 or 10×10^6 C-CAR168 CAR-T cells/mouse was well tolerated in B-NDG tumor bearing mice, and C-CAR168 significantly inhibited the growth of K562-CD20-BCMA tumor cells in a dose-dependent manner.

Example 6 Antigen Specificity of Anti-CD20/BCMA CARs

[0249] In the membrane protein array, genetic engineering methods are used to construct the full-length cDNA sequences of human membrane proteins into expression vectors, which are then transiently transfected into HEK293T cells and arranged into an array by using microfluidic technology or chip printing technology. It is a high-throughput screening technology for studying the interaction between test substances and membrane proteins.

[0250] To examine the affinity and specificity of the anti-CD20/BCMA CARs, we used a membrane protein array assay to evaluate the risk of off-target binding between the antigen-binding domain of C-CAR168 and 5220 human cell membrane proteins.

[0251] A chimeric rabbit monoclonal antibody, C-CAR168 scFv-RabFc, was generated by linking the anti-CD20 scFv (e.g., derived from the Ofatumumab mAb) and the anti-BCMA scFv (e.g., derived from the BCMA-20 mAb) in frame with a rabbit IgG Fc region. The chimeric antibody was added at a concentration of 20 µg/mL to the H E K293T cell array transiently transfected with 5220 membrane proteins. Flow cytometry results show that C-CAR168 scFv-RabFc bound strongly to human CD20 and BCMA (FIG. 8A). The average fluorescence intensity of its binding to CD20 and BCMA in flow cytometry was about 60-fold and 110-fold of that of the negative control group, respectively (FIG. 8B). In addition to CD20 and BCMA, C-CAR168 scFv-RabFc showed specific binding to FCGR1A (FIG. 8B), and the average fluorescence intensity was 2.5 times that of the negative control group. This is mainly due to the binding between FCGR1A and the rabbit-derived Fc of the recombinant protein; so there is no relevant risk in clinical applications. C-CAR168 scFv-RabFc showed weak binding to ITGB2-ITGAM and ITGB2-ITGAL heterodimers, and the average fluorescence intensity was 2 to 3 times that of the negative control group. For other proteins discovered in the preliminary screening (MPZ, F11R, CLEC2B and MC2R), the average fluorescence intensity binding to C-CAR168 scFv-RabFc did not change with

concentration. At the concentrations of 20 µg/mL and 5 µg/mL, it did not exceed 2 times that of the negative control group, so the possibility of these proteins binding specifically to C-CAR168 scFv was low or minimal.

[0252] To test whether ITGB2-ITGAM and ITGB2-ITGAL heterodimers expressed on the cell membrane can be recognized by C-CAR168 CAR-T cells to activate downstream events, C-CAR168 was co-cultured with 293T cells transfected with ITGB2-ITGAM or ITGB2-ITGAL. Expression of CD137 on C-CAR168 CAR-T cells, as well the levels of IFN-γ, TNF-α, IL-2 and other cytokines in the cell culture supernatant, were assayed. 293T cells transfected with empty vector were used as negative control, and 293T cells transfected with CD20 and BCMA were used as positive control.

[0253] CD137 (4-1BB) is a cell surface marker for antigen-specific activation of T cells. The antigen-specific activation of CAR-T cells can be assessed by detecting the up-regulation of CD137 expression on the cell surface. The experiment found that after three batches of C-CAR168 cells were co-cultured with cells expressing CD20 and BCMA, the proportion of 4-1BB-positive cells increased compared with non-transduced T cells ("NT"). After co-culturing with those expressing ITGB2-ITGAM and ITGB2-ITGAL, the proportion of 4-1BB positive cells was not significantly different from that in the non-transduced T cell group ("NT") (FIG. 8D, left panel), indicating that C-CAR168 does not bind specifically to ITGB2-ITGAM or ITGB2-ITGAL in vitro.

[0254] Cytokines in the cell culture supernatant were assayed, and the results showed that C-CAR168 CAR-T cells secreted high levels of IFN-γ when co-cultured with cells expressing CD20 or BCMA. When co-cultured with cells expressing ITGB2-ITGAM or ITGB2-ITGAL, compared with non-transduced T cells, the concentrations of IFN-γ in the supernatant did not increase significantly (FIG. 8D, right panel). The results further showed that C-CAR168 did not specifically recognize ITGB2-ITGAM and ITGB2-ITGAL in vitro.

[0255] In summary, the membrane protein array and in vitro co-culture results show that the antigen-binding domain of C-CAR168 binds strongly to human CD20 and BCMA, and has no other non-specific binding sites. The membrane protein array study identified that C-CAR168 has no cross-reactivity against membrane proteome except weak binding to two heterocomplexes.

Example 7C-CAR168 Shows Robust Potency Against Autologous B Cells from SLE Patients

[0256] To study CAR-T therapies for the treatment of autoimmune diseases, such as SLE, we evaluated the efficiency of the CAR-T cells to deplete autoreactive B cells. We will also study the efficacy of the CAR-T cells on remission and survival of a lupus model.

Efficiency of C-CAR168 to Eliminate Pan B Cells from Lupus Patients In Vitro

[0257] 10-15 mL of peripheral blood samples from eight patients with SLE were collected. The patients had different activity and autoantibody profile, displayed different organ damage (patients with lupus nephritis were preferable), and underwent different treatment, to represent the heterogeneous nature of lupus patients. Patients who recently received B cell depleting antibodies were excluded.

[0258] For each sample, part of the blood was used to isolate T cells for CAR-T production, and the remaining blood was used to isolate pan B cells as target for a cytolytic assay. T cells isolated from eight SLE patients were transduced by lentiviral vectors encoding C-CAR168 and tested for CAR expression. T cell samples from 8 SLE patient samples were successfully transduced and expanded well for function assays (FIG. 10A).

[0259] C-CAR168 CAR-T cells generated from 8 patient samples, or non-transduced (NT) T cells, were co-cultured with target cell lines expressing CD20 or/and BCMA. K562 is negative for both CD20 and BCMA; MM.1S is a multiple myeloma cell line which is BCMA-positive. After 24 hours, co-culture supernatants were collected for ELISA (enzyme-linked immunosorbent assay) to assess the IFN-γ levels. Result from one representative sample of 8 patients is shown in FIG. 10B. Thus, C-CAR168 cells generated from SLE patient samples showed robust activity against target cells expressing CD20 and BCMA.

[0260] Isolated pan B cells isolated from 8 patient samples were co-cultured with autologous C-CAR168 CAR-T cells, or non-transduced (NT) T cells, at the indicated E:T (effector to target) ratios. After 24 hours, co-culture supernatants were collected for ELISA to assess the IFN-γ levels. Cytotoxicity was determined by fluorescence-activated cell sorting (FACS) and calculation of the depletion of the percentage of viable CD19+ pan B cells. The cytotoxicity of B cells was calculated by the following formula: Percentage of lysis (%)=(1-(viable CD19+ cell fraction of the C-CAR168 coculture/viable CD19+ cell fraction of UT coculture))×100. Results from one representative sample of 8 patients are shown in FIGS. 10C and 10D. Pan B cells isolated from 8 SLE patient samples were recognized and lysed by autologous C-CAR168 cells. The results confirmed the efficiency of C-CAR168 CAR-T cells to deplete peripheral B cells from lupus patients in the in vitro setting.

Efficiency of the CAR-T to Eliminate ABCs from Lupus Patients In Vitro

[0261] The efficiency of the CAR-T to eliminate ABCs, the essential subset of pathogenic B cells, from lupus patients in vitro will be studied.

[0262] Blood samples or PBMCs from lupus patients will be processed for ABC's differentiation and CAR-T production as well as functional analysis.

[0263] The study will confirm the efficiency of the CAR-T cells to deplete ABCs from lupus patients in the in vitro setting.

Efficiency of the CAR-T to Deplete B Cells and the Therapeutic Efficacy In Vivo

[0264] The efficiency of the CAR-T to deplete B cells and its therapeutic efficacy will be evaluated in vivo with a humanized mouse model of SLE. CD34+ stem cell humanized mice will be obtained. 2 or more mice will be sacrificed to collect spleens with aseptic technique. T cells will then be isolated from the spleens for CAR-T production. The remaining mice will be used to induce the onset of lupus disease, and upon successful induction, mice will be divided into groups to receive CAR-T or control treatment (for example, non-transduced T cells). Blood samples will be obtained from the mice periodically to monitor the persistence of CAR-T cells, as well as efficiency of B cell depletion (including ABCs) by FACS. The sera samples will be used to measure the titers of various autoantibodies.

Urine samples will also be routinely collected to measure the levels of proteinuria. At the end of the study, or in case an animal dies early (presumably in control group), tissues will be collected for histology, for example, to examine the deposition of immune complex in the kidney and the severity of nephritis. The presence of B cells or plasma cells in diseased tissue will also be examined. Survival curves will be generated to compare the effect of CAR-T versus control treatment.

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- [0273] The structures of the anti-CD20/BCMA CARs, TO 1-4 and TOBL1-4, are shown in Table 1.

TABLE 1

Anti- CD20/BCMA CAR	scFv V _H /V _L order	CAR structure
TN-OF-B20-L1 (TOBL1, or C-CAR168)	OF(V _L -V _H) - B20(V _L -V _H)	SP - OF V _L - linker 1 - OF V _H - linker 2 - B20 V _L - linker 3 - B20V _H - CD8 hinge - CD8 TM - 41BB - CD3z
TN-OF-B20-L2 (TOBL2)	OF(V _H -V _L) - B20(V _L -V _H)	SP - OF V _H - linker 1 - OF V _L - linker 2 - B20 V _L - linker 3 - B20V _H - CD8 hinge - CD8 TM - 41BB - CD3z
TN-OF-B20-L3 (TOBL3)	OF(V _H -V _L) - B20(V _H -V _L)	SP - OF V _H - linker 1 - OF V _L - linker 2 - B20 V _H - linker 3 - B20V _L - CD8 hinge - CD8 TM - 41BB - CD3z
TN-OF-B20-L4 (TOBL4)	OF(V _L -V _H) - B20(V _H -V _L)	SP - OF V _L - linker 1 - OF V _H - linker 2 - B20 V _H - linker 3 - B20V _L - CD8 hinge - CD8 TM - 41BB - CD3z
TN-OF-B20-1 (TOB1)	OF(V _L -V _H) - B20(V _H -V _L)	SP - OF V _L - linker 1 - OF V _H - linker 2 - B20 V _H - linker 3 - B20V _L - IgG4 hinge - CD28 TM - 41BB - CD3z
TN-OF-B20-2 (TOB2)	OF(V _L -V _H) - B20(V _L -V _H)	SP - OF V _L - linker 1 - OF V _H - linker 2 - B20 V _L - linker 3 - B20V _H - IgG4 hinge - CD28 TM - 41BB - CD3z
TN-OF-B20-3 (TOB3)	OF(V _H -V _L) - B20(V _L -V _H)	SP - OF V _H - linker 1 - OF V _L - linker 2 - B20 V _L - linker 3 - B20V _H - IgG4 hinge - CD28 TM - 41BB - CD3z
TN-OF-B20-4 (TOB4)	OF(V _H -V _L) - B20(V _H -V _L)	SP - OF V _H - linker 1 - OF V _L - linker 2 - B20 V _H - linker 3 - B20V _L - IgG4 hinge - CD28 TM - 41BB - CD3z

SEQUENCES

TN-OF-B20-L1 (TOBL1, or C-CAR168)
CD8a SP nucleic acid sequence (63 nt) (SEQ ID NO: 1)
atggccttaccagtgaccgccttgccctgcccgtggccctgtctccacggccaggcc
CD8a SP amino acid sequence: (SEQ ID NO: 2)
MALPVTALLLPLALLLHAARP
OF V_L nucleic acid sequence (321 nt) (SEQ ID NO: 3)
GAAATTGTGTTGACACAGTCTCCAGCCACCTGTCTTCAGGGAAAGAGCC
ACCCTCTCCTGCAGGGCCAGTCAGAGTGTAGCAGCTACTTAGCCTGGTACCAACAG

-continued

Linker-3 amino acid sequence:

(SEQ ID NO: 14)

GGGGSGGGSGGGGS

B20 V_H nucleic acid sequence (363 nt)

(SEQ ID NO: 15)

Gagggtcagctggtgaggctccggcgccggcctggtcagccccggggctccctggggctgtctgcggccgacccgggttacacccatctccatcaccacccggcgaccacgcatctacgcccactccgtgaaggccggttaccatctccggacaacgccaagaacacccctgtacactgcagatgaactccctgcggccgg
gacaccgcgtgtactactgcgtgcggcacggctactacgacggctaccacccgttacactggggccagggaccctggtaccctg
tcctcc

B20 V_H amino acid sequence:

(SEQ ID NO: 16)

EVQLVESGGGLVQPGGSLRLSCAASGFTFSNFDMAWVRQAPGKGLVWVSSITTGA

DHAIYADSVKGRFTISRDNAKNTLYLQMNSLRAEDTAVYYCVRHGYDGYHLFDY

WGQGTLTVSS

CD8a hinge nucleic acid sequence (165 nt)

(SEQ ID NO: 17)

Ttcgtccgggtttctgccagcgaagccaccacgacgccagccggccgaccaccaacaccggggccaccatcgctgcagcc
ctgtccctgcgcccagaggcgtgccggccagggcgccggggggcgactgcacacgaggggctggacttcgcctgtat

CD8a hinge amino acid sequence:

(SEQ ID NO: 18)

FVPVFLPAKPTTPAPRPPTPAFTIASQPLSLRPEACRPAAGGAVHTRGLDFACD

CD8a TM nucleic acid sequence (72 nt)

(SEQ ID NO: 19)

Atctacatctggccgccttggccggacttgtgggtcttctctgtactggttatcaccccttactgc

CD8a TM amino acid sequence:

(SEQ ID NO: 20)

IYIWAPLAGTCGVLLSLVITLYC

4-1BB nucleic acid sequence (126 nt)

(SEQ ID NO: 21)

Aaacggggcagaaaactctgtatataattcaaacaaccattatgagaccagtacaaactactcaagaggaaagatggcttagctgcc
gatttccagaagaagaaggaggatgtgaactg

4-1BB amino acid sequence:

(SEQ ID NO: 22)

KRGRKKLLYIFKQPFMMPVQTTQEEEDGCSCRFPEEEggcel

CD3z nucleic acid sequence (336 nt)

(SEQ ID NO: 23)

Agagtgaagttcagcaggagcgcagacgccccccgttaccacgacggggccagaaccaggctataacgagctcaatctaggacagaaga
gaggagtacgtttggacaagagacgtggccggaccctgagatggggaaagccgagaaggaaagacccctcaggaaggcctg
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ggcccttaccagggtctcagtgccaccaaggacacctacgacgcccttacatgcaggccctgccccctcgctaa

CD3z amino acid sequence:

(SEQ ID NO: 24)

RVKFSRSADAPAYQQQNQLYNELNLGRREYDVLDKRRGRDPEMGGKPRRKNP

QEGLYNELQDKDMAEAYSEIGMKGERRGKHDGLYQGLSTATKDTYDALHMQ

ALPPR

TOBL1 nucleic acid sequence (2247 nt)

(SEQ ID NO: 25)

atggccttaccagtgcacccctgtccctggccgtggcccttgcgtccacgcggccaggccgGAAATTGTGTTGACACA

GTCTCCAGCCACCCCTGTCTTGTCTCCAGGGAAAGAGGCCACCCCTCTCCTGCAGGGC

CAGTCAGAGTGTAGCAGCTACTTAGCCTGGTACCAACAGAACCTGGCCAGGCTC

- continued

-continued

CD8a hinge nucleic acid sequence (165 nt)

(SEQ ID NO: 35)

Ttcgtgcgggtttccgtccagcgaagcccaccacgacgcccagcgcggcgaccacaacaccggcgcccaccatcgctcgacggcc

ctgtccctgcgcgcagggcgtccggccagcggcgccggggggcgactgcacacgaggggctggacttcgtgtat

CD8a TM nucleic acid sequence (72 nt)

(SEQ ID NO: 36)

Atctacatctggggccccctggccggacttggggcttctctgtcactggttatcaccccttactgc

4-1BB nucleic acid sequence (126 nt)

(SEQ ID NO: 37)

Aaacggggcagaaaactctgtatataattcaacaaccattatgagaccagtacaaactactcaagaggaaagatggctgttagctgcc

gatttccagaagaagaaggaggatgtgaactg

CD3z nucleic acid sequence (336 nt)

(SEQ ID NO: 38)

Agagtgaagttcagcaggagcgcagacgcccccgcttaccagcaggccagaaccagctataacgagctaatctaggacgaga

gaggagtacgttttgacaagagacgtggccggaccctgagatggggaaagccgagaaggaaaccctcaggaaggcctg

tacaatgaactgcagaaagataagatggcgaggcctacagttagatggatgaaaggcgagcgcggaggggcaaggggcaacat

ggcccttaccagggtctcgtacagccaccaaggacacctacgcgccttacatgcaggccctgcggccctcgctaa

TOBL2 nucleic acid sequence (2247 nt)

(SEQ ID NO: 39)

atggccttaccagtgaccgcctgtctctgcgtggcttgcgtctccacggccaggccGAAGTGCAGCTGGTGGA

GTCTGGGGAGGCTTGGTACAGCCTGGCAGGTCCCTGAGACTCTCTGTGCAGCCTC

TGGATTCACCTTAATGATTATGCCATGCACTGGTCCGGCAAGCTCCAGGGAAAGG

CCTGGAGTGGTCTCAACTATTAGTTGAATAGTGGTCCATAGGCTATCGGGACTC

TGTGAAGGGCCATTCAACCCTCCAGAGACAACGCCAAGAAGTCCCTGTATCTC

AAATGAACAGTCTGAGAGCTGAGGACACGGCTTGATTACTGTCAAAGATA

CACTACGGCAACTACTACTACGGTATGGACGCTGGGGCCAAGGGACACGGTCAC

CGTCTCCTCAGGCAGTACTAGGGTGGCTCCGGGGCGGTTCCGGTGGGG

GCAGCAGCGAAATTGTGTTGACACAGTCTCCAGCCACCCCTGTCTTGCTCCAGGG

AAAGAGCCACCCCTCCTGCAGGGCAGTCAGAGTGTAGCAGCTACTTAGCCTGGT

ACCAACAGAAAAGTGGCAGGCTCCCAGGCTCCTCATATGATGCATCCAACAGG

GCCACTGGCATCCCAGCCAGGTTCACTGGCAGTGGCTGGGACAGACTCCTACTCTC

ACCATCAGCAGCCTAGAGCCTGAAGATTTGCAGTTATTACTGTCAGCAGCGTAGC

AACTGGCGATCACCTCGGCCAAGGGACACGACTGGAGATAAAGGAGGTGGTGG

ATCCGacatccagatgacccagatcccccttccctgtccgcctccgtggcgaccgggtgaccatcacctgcggccctccaggg

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agaaaactcctgtatataattcaaacaaccatttatgagaccagtacaaactactcaagaggaagatggctgtagctgccgattccagaagaag
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 agctcaatcttaggacgaagagaggatcgcgtttggacaagagacgtggccggaccctgagatgggggaaagccgagaaggaa
 gaaccctcaggaaggcctgtacaatgaactgcagaaaagataagatggcggaggcctacagttagatggatgaaaggcggagccgg
 aggggcaaggggcaacgatggccttaccagggtctcgtacagccaccaaggacacctacgacgccttcacatgcaggccctgcccc
 tcgctaa

TOBL2 amino acid sequence:

(SEQ ID NO: 40)

MALPVVTALLPLALLHAARPEVQLVESGGGLVQPGRLSRLSCAASGFTFNDYAM
 HWVRQAPGKGLEWWSTISWNNSGSIYGADSVKGRFTISRDNAKSLYLQMNSLRAE
 DTALYYCAKDIQYGNYYGMDVWGQTTTVSSGSTSGGSGGSGGGSSSEIVL
 TQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASN RATGIPAR
 FSGSGSGTDFTLTISLEPEDFAVYYCQQRSNWPITFGQGTRLEIKGGGSDIQMTQ
 SPSSLSASVGDRVTITCRASQGISNYLNWYQQKPGKAPKPLIYYTSNLQSGVPSRFSG
 SGSGTDTLTISSLQPEDFATYYCMGQTISSYTFGQGKLEIKGGGSGGGSGGG
 GSEVQLVESGGGLVQPGGSLRLSCAASGFTFSNFDMAWVRQAPGKGLVVSSITT
 GADHAIYADSVKGRFTISRDNAKNTLYLQMNSLRAEDTAVYYCVRHGYYDGYHLF
 DYWGQGTLVTVSSFPVPFLPAKPTTTPAPRPPTPAPTIAQSPLSLRPEACRPAAAGGA
 VHTRGLDFACDIYIWAPLAGTCGVLLSLVITYCRGRKLLYIFKQPFMRPVQT
 TQEEDGCSCRFPPEEEGGCELRVKFSRSADAPAYQQQNQLYNELNLGRREYDV
 LDKRRGRDPMEGGKPRRKNPQEGLYNELQDKMAEAYSEIGMKGERRRGKHD
 GLYQGLSTATKDTYDALHMQALPPR

TN-OF-B20-L3 (TOBL3)

CD8a SP (63 nt) nucleic acid sequence

(SEQ ID NO: 41)

Atggccttaccagtgaccgccttgccctgcggctggcccttgcgtccacgcgcgcaggccg

OF V_H nucleic acid sequence

(SEQ ID NO: 42)

GAAGTGCAGCTGGTGGAGTCTGGGGAGGCTTGTACAGCCTGGCAGGTCCCTGAG
 ACTCTCCTGTGCAGCCTCTGGATTCACCTTAATGATTATGCCATGCACTGGTCCGG
 CAAGCTCCAGGGAAAGGGCCTGGAGTGGGTCTCAACTATTAGTTGGAATAGTGGTCC
 ATAGGCTATGCGGACTCTGTGAAGGGCGATTCAACATCTCCAGAGACAACGCCAA
 GAAGTCCCTGTATCTGCAAATGAAACAGTCTGAGAGCTGAGGACACGGCCTTGTATT
 CTGTGCAAAAGATAACAGTACGGCAACTACTACTACGGTATGGACGTCTGGGGCC
 AAAGGGACCACGGTCACCGTCTCCTCA

Linker-1 nucleic acid sequence

(SEQ ID NO: 43)

GGCAGTACTAGCGGTGGCTCGGGGGCGGTTCCGGTGGGGCGGCAGCAGC

OF V_L nucleic acid sequence

(SEQ ID NO: 44)

GAAATTGTGTTGACACAGTCTCCAGCCACCCCTGTCTTGCTCCAGGGAAAGAGCC
 ACCCTCTCCTGCAGGGCAGTCAGAGTGTAGCAGCTACTTAGCCTGGTACCAACAG
 AACCTGGCCAGGCTCCCAGGCTCTCATCTATGATGCATCCAACAGGGCACTGGC
 ATCCCAGCCAGGTTAGGGCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGC

-continued

AGCCTAGAGCCTGAAGATTTGCAGTTATTACTGTCAGCAGCGTAGCAACTGGCCG

ATCACCTCGGCCAAGGGACACGACTGGAGATTA

Linker-2 nucleic acid sequence

(SEQ ID NO: 45)

GGAGGTGGTGGATCC

BCMA-20 scFv (729 nt):

B20 V_H nucleic acid sequence (363 nt)

(SEQ ID NO: 46)

Gagggtcagctgggtggagtccggccggcgttgcagccccggggctccctgcggctgtctgcggccgttcggcttctc
caacttcgacatggcctgggtgcggcaggccccggcaagggcctgggtgggtgtccatcaccaccggcgccgaccacccatct
acgcccactccgtgaagggccggttaccatctccggacaacgccaagaacaccctgtacactgcagatgaactccctgcggccgag
gacaccgcgtgtactactgcgtgcggcacggctactacgacggctaccacctgttcgactactggggcagggcacccctggtgaccctg
tcctcc

Linker-3 nucleic acid sequence (45 nt)

(SEQ ID NO: 47)

Ggtggcggtggctcgccgggtgggtcggtggcgccggatct

B20 V_L nucleic acid sequence (321 nt)

(SEQ ID NO: 48)

Gacatccagataccctgtcccccctccctgtccgcctccgtggcgaccgggtgaccatcacctgcgggcctccaggcatctcc
aactacatgtaccagcagaagccccggcaaggccccaaagccctgtatctactacacccatccaaacctgcagtccggcgtccctcc
cggttctccggctccggctccggcaccgactacaccctgaccatctccctgcagcccaggacttcgcccacctactgcattggcc
agaccatctccctacacccctggccaggcaaccaagctggagatcaag

CD8a hinge nucleic acid sequence (165 nt)

(SEQ ID NO: 49)

Ttcgtgcgggtttctgtccagcgaagccaccacgacgcggcgcaccaccaacccggcggccaccatcgctgcagcc
ctgtccctgcgcccagaggcgtgccggcagccggggggccgcagtgcacacgaggggctggacttcgcctgtgat

CD8a TM nucleic acid sequence (72 nt)

(SEQ ID NO: 50)

Atctacatctggcgccttgccggacttgtgggtctttctctgtactgttatcaccccttaactg

4-1BB nucleic acid sequence (126 nt)

(SEQ ID NO: 51)

Aaacggggcagaaaactccgttatattcaaacaaccattatgagaccagtacaaactactcaagaggaagatggctgtagctcc
gatttccagaagaagaaggaggatgtgaactg

CD3z nucleic acid sequence (336 nt)

(SEQ ID NO: 52)

Agagtgaagttcagcaggagcgcagacgcccccgcttaccacgcaggccagaaccaggctataacgagtcataatctaggacaga
gaggagtagatgtttggacaagagacgtggccggaccctgagatggggaaagccgagaaggaagaaccctcaggaaggctg
tacaatgactgcagaaagataagatggccggggctacagttagatggatgaaaggcgcggccggaggggcaagggcacat
ggccttaccagggtctcagtagccaccaaggacacccatgcagcccttacatgcaggccctgcggccctcgctaa

TOBL3 nucleic acid sequence

(SEQ ID NO: 53)

atggccttaccagtgaccgccttgcctgtccgtccgccttgcgtccacggccaggccGAAGTGCAGCTGGTGGA

GTCTGGGGAGGCTTGGTACAGCCTGGCAGGTCCCTGAGACTCTCCTGTGCAGCC

TGGATTCACCTTAATGATTATGCCATGCACTGGTCCGGCAAGCTCCAGGGAAAGG

CCTGGAGTGGTCTCAACTATTAGTTGGAAATAGTGGTCCATAGGCTATGCGGACTC

TGTGAAGGGCCATTCAACCATCTCCAGAGACAACGCCAAGAAGTCCCTGTATCTGC

AAATGAAACAGTGTGAGAGCTGAGGACACGGCTTGATTACTGTGCAAAGATA

CACTACGGCAACTACTACTACGGTATGGACGTCGGGGCCAAGGGACCACGGTCAC

CGTCTCCTCAGGCAGTACTAGCGGTGGCTCCGGGGCGGTTCCGGTGGGGCG

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GCAGCAGCGAAATTGTGTTGACACAGTCTCCAGGCCACCCCTGCTTGTCTCCAGGG
 AAAGAGCCACCCCTCCTGCAGGGCAGTCAGAGTGTAGCAGCTACTTAGCCTGGT
 ACCAACAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGATGCATCCAACAGG
 GCCACTGGCATCCCAGCCAGGTTCACTGGCAGTGGGTCTGGGACAGACTTCACTCTC
 ACCATCAGCAGCCTAGGCCTGAAGAGTTTGCACTTATTACTGTCAGCAGCGTAGC
 AACTGGCCGATCACCTCGGCCAAGGGACACGACTGGAGATTAAAGGAGGTGGTGG
 ATCCGaggtgcagctgggagttccggcggeggcctggcagccccggcgccctccggcttca
 ccttcctccaacttcgacatggcctgggtgcggcaggccccggcaaggcctgggtgtgggttccatcacccaccggcgccgaccac
 gccatctacgccgactccgtgaaggccgggttccatctcccccggacaacccctgtacactgcagatgaactccctgg
 gccgaggacaccggcggtgactactgcgtgeggcaaggctactacgacggctaccacctgttgcactactggggccagggcaccctgg
 gaccgtgttccctccGgtggcggtggctgggggggtgggggtggcgggatctGacatccagatgaccaggccccctcc
 ctgtccgcctccgtggcgaccatcacctgcccggccctccaggcatctcaactacctgaactggtaccaggagaagccc
 ggcaaggcccccaagccctgtatctactacacccatctccggcgtgcggccctccgggttccggcggccatccggcaccac
 tacaccctgaccatctccctccgtggcgaggacttgcacccatctactgcattggccagaccatctcccttacacccatccggcagg
 caccaaaggctggagatcaagtgcgtggcgttccctgcaccgcgaaaggccaccacgacggccagcggccgaccaccacaccgg
 accatcgcgtcgccggccctgtccctgcggccagaggcgtgcggccagggggggcactgcacacgagggggtggacttc
 gcctgtatatactatctggcgcccttggcgccggacttgcgtgggttccctccgtactgggttaccccttactgc
 agaaactcctgtatataattcaaacaaccattatgagaccatgaaactactcaagaggaatggctgtactgc
 aacccctcagaaggccgttacaatgaactgcagaaagataagatggcggaggccatgc
 agatggatgaaaggccggccgg
 aggggcaaggggacgatggccttaccagggtctcagtagccaccaaggacacctacgaccccttacatgc
 caggccctgcccc
 tcgctaa

TOBL3 amino acid sequence:

(SEQ ID NO: 54)

MALPVTALLPLALLLHAARPEVQLVESGGGLVQPGRSLRLSCAASGFTFNDYAM
 HWVRQAPGKGLEWVSTISWNNSIGYADSVKGRFTISRDNAKKSLYLQMNSLRAE
 DTALYYCAKDIQYGNYYYGMDVWGQTTVTVSSGSTSGGSGGSGGGSSSEIVL
 TQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRTGIPAR
 FSGSGSGTDFTLTISLEPEDFAVYYCQQRSNWPITFGQGTRLEIKGGGSEVQLVE
 SCGGGLVQPQGGSLRLSCAASGFTFSNFDMAVRQAPGKGLVWVSSITTGADHAIYA
 DSVKGRFTISRDNAKNTLYLQMNSLRAEDTAVYYCVRHGYYDGYHLFDYWGQGT
 LTVVSSGGGGGGGGGGSDIQMTQSPSSLASVGDRVITCRASQGISNYLNW
 YQQKPGKAPKPLIYYTSNLQSGVPSRFSGSGSGTDYTLTISSLQPEDFATYYCMQQT
 ISSYTFQGQGTKLEIKFVPVFLPAKPTTPAPRPPTPAPTIAQPLSLRPEACRPAAGG
 AVHTRGLDFACDIYIWAPLAGTCGVLLSLVITLYCKRGRKLLYIFKQPFMRPVQ
 TTQEEDGCSRFPIEEEGGCELRVKFDSADAPAYQQGQNQLYNELNLRREYD
 VLDKRRGRDPEMGGKPRRKNPQEGLYNELQDKMAEAYSEIGMKGERRRGKH
 DGLYQGLSTATKDTYDALHMQALPPR

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TN-OF-B20-L4 (TOBL4)
 CD8a SP nucleic acid sequence (63 nt) (SEQ ID NO: 55)

```
Atggccttaccagtgaccgcctgtccctgccgtggccttgtctccacgcccaggccg
```

OF V_L nucleic acid sequence (SEQ ID NO: 56)

```
GAAATTGTGTTGACACAGTCTCAGCCACCCCTGTCTTGTCAGGGAAAGAGCC  
ACCCCTCTCCTGCAGGGCCAGTCAGAGTGTAGCAGCTACTTAGCCTGGTACCAACAG  
AACACTGGCCAGGCTCCAGGCTCCTCATCTATGATGCATCCAACAGGGCACTGGC  
ATCCCAGCCAGGTTCACTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGC  
AGCCTAGAGCCTGAAGATTTGCAGTTTATTACTGTCAGCAGCGTAGCAACTGGCCG  
ATCACCTTCGGCCAAGGGACACGACTGGAGATAAA
```

Linker-1 nucleic acid sequence (SEQ ID NO: 57)

```
GGCAGTACTAGCGGTGGTGGCTCGGGGGCGGTCCGGTGGGGCGGCAGCAGC
```

OF V_H nucleic acid sequence (SEQ ID NO: 58)

```
GAAAGTGCAGCTGGTGGAGTCTGGGGAGGCTGGTACAGCCTGGCAGGTCCCTGAG  
ACTCTCCTGTGCAGCCTCTGGATTACCTTAATGATTATGCCATGCACTGGTCCGG  
CAAGCTCCAGGGAAAGGGCCTGGAGTGGGTCTCAACTATTAGTTGGAATAGTGGTTCC  
ATAGGCTATGCGGACTCTGTGAAGGGCGATTCAACCATCTCCAGAGACAACGCCAA  
GAAGTCCCTGTATCTGCAAATGAAACAGTCTGAGAGCTGAGGACACGGCCTTGTATT  
CTGTGCAAAAGATAACAGTACGGCAACTACTACTACGGTATGGACGTCTGGGGCC  
AAGGGACCACGGTCACCGTCTCCTCA
```

Linker-2 nucleic acid sequence (SEQ ID NO: 59)

```
GGAGGTGGTGGATCC
```

BCMA-20 scFv (729 nt):
 B20 V_H nucleic acid sequence (363 nt) (SEQ ID NO: 60)

```
Gaggtgcagctggtgaggatccggcgccggctggtcagccggccggctccctggggctgtcctgcgcggccctccggcttcacccatc  
caacttcgacatggcctgggtcgccgaggccccccggcaaggccctgggtgggttcctccatcaccacccggccgaccacccatc  
acggcgactccgtgaaggccgggttccatctccggacaacgccaagaacacccctgtacctgcagatgaactccctgcggcccgag  
gacaccggcgtgtactactgcgtgcggcacggctactacgacggctaccacctgttcgactactggggccagggaccctggtgaccgt  
tcctcc
```

Linker-3 nucleic acid sequence (45 nt) (SEQ ID NO: 61)

```
Ggtggcgtggctcgccgggtgggtcggtggatct
```

B20 V_L nucleic acid sequence (321 nt) (SEQ ID NO: 62)

```
Gacatccagataccagttccctccctgtccgcctccgtggcgaccgggtgaccatcacctgcggccctcccgatctcc  
aactacctgaactggtaccagcagaagccggcaaggcccccaagccctgtactactacacccatccaaacctgcagtcggcggtgc  
cggttcctccgtccggctccggcacggactacaccctgaccatctccctccatcagccgaggacttcgcccacactactgc  
agaccatctccctacacccttcggccaggcaccaagctggagatcaag
```

CD8a hinge nucleic acid sequence (165 nt) (SEQ ID NO: 63)

```
Ttcgtgcgggtttctgcgcagcgaagccaccacgacgcggcagccggccaccatcgctcgacacgaggggctggacttcgc  
ctgtccctgcgcaggcgtggccaggccggccggggggccgcagtcacacgaggggctggacttcgc
```

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CD8a TM nucleic acid sequence (72 nt) (SEQ ID NO: 64)
Atctacatctggcgcccttgccggacttgtgggtccttcctgtcactggttatcaccccttactgc

4-1BB nucleic acid sequence (126 nt) (SEQ ID NO: 65)
Aaacggggcagaaaagaaaactctgtatatatccaacaaccattatgagaccagtacaaactactcaagaggaagatggctgttagctgcc
gattccagaagaagaaggaggatgtgaactg

CD3z nucleic acid sequence (336 nt) (SEQ ID NO: 66)
Agagtgaagttcagcaggagcgcagacgccccccgcgtaccagcagggccagaaccagctataacgagctaatctaggacaga
gaggagtacgtttggacaagagacgtggccggaccctgagatgggggaaagccgagaaggaacaacctcaggaaggcctg
tacaatgaactcagaaagataagatggcggggcctacagttagatggatgaaaggcggcgcggggcaagggcacat
ggccttaccagggtctcagtagccaccaaggacacctacgacgccttacatgcaggccctgccccctcgctaa

TOBL4 nucleic acid sequence (2247 nt) (SEQ ID NO: 67)
atggccattaccagtgaccgcctgtctctgcccgtggcctgtgtgtccacgcggcaggccg GAAATTGTGTTGACACA
GTCTCCAGCCACCCCTGTCTTGTCTCCAGGGAAAGAGGCCACCCCTCTCCTGCAGGGC
CAGTCAGAGTGTAGCAGCTACTTAGCCTGGTACCAACAGAAACCTGGCCAGGCTC
CCAGGCTCCTCATCTATGATGCATCCAACAGGCCACTGGCATCCCAGGCCAGGTTCA
GTGGCAGTGGTCTGGACAGACTTCACTCTCACCATCAGCAGCCTAGAGCCTGAA
GATTTGCAGTTTAACTGTCAAGCGTAGCACTGGCGATCACCTTCGGCAA
GGGACACGACTGGAGATTAAGGCAGTACTAGCGGTGGCTCCGGGGCGGTTC
CGGTGGGGCGCAGCAGCGAAGTGCAGCTGGTGGAGTCTGGGGAGGCTTGGTAC
AGCCTGGCAGGCCCCGTGAGACTCTCTGTGCAGCCTCTGGATTCACTTTAATGATT
ATGCCATGCACTGGTCCGGCAAGCTCCAGGGAAAGGGCCTGGAGTGGTCTCAACT
ATTAGTTGGAATAGTGGTCCATAGGCTATGCGGACTCTGTGAAGGGCCGATTCAAC
ATCTCCAGAGACAACGCCAAGAAGTCCCTGTATCTGCAAATGAACAGTCTGAGAGC
TGAGGACACGGCTTGTATTACTGTGCAAAAGATAACAGTACGGCAACTACTACTA
CGGTATGGACGTCTGGGCCAAGGGACCACGGTCACCGTCTCTCAGGAGGTGGT
GATCCgaggtcagctggtagtccggcgccgtggcagccccggggctgtcctgcggccctccggcttc
acattctccaacttcgacatggcctgggtggcaggccccggcaaggccctgggtgggtcctccatcaccacggcggcaccac
ggcatctacgcgcactccgtgaaggccgggttaccatctccgggacaacgccaagaacaccctgtacactgcagatgaactccctgcgg
ggcaggacaccggcgtgtactactgcgtggcggcaggccctggcgttgcactactggggccagggcaccctgg
gaccgtgtccctcGgtggcggtggctgggggggtgggtgggtggcggatctGacatccagatgaccatggccatccctcc
ctgtccgcctccgtggcgaccgggtgaccatcacctgcggccgttccctccggatctccacttgcactgggttaccagcagaagccc
ggcaaggcccccaagccctgtatctactacacccctcaacccgttccctccggatctccggatccggcaccgac
tacaccctgaccatctccctgcagcccgaggactcgccacccactactgcattggccagaccatctcccttacacccctggccagg
caccatggagatcaagttcgtggcgttccctgcggccaggccgtggccggccagggggggccgactgcacacgagggggctggacttc
ccctgtatctacatctggcgcccttgccggacttgtgggtccttcctgtcactgggttatcaccccttactgcaaacggggcagaa
agaaactctgtatatatccaacaaccattatgagaccagtacaaactactcaagaggaagatggctgttagctgccattccagaagaag
aagaaggaggatgtgaactgAgagtgaagttcagcaggagcgcagacgccccccgcgtaccagcagggccagaaccagctataacg
agctcaatctaggacgaagagaggatgcgtttggacaagagacgtggccggaccctgagatgggggaaagccgagaaggaa

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Linker-2 nucleic acid sequence

(SEQ ID NO: 73)

GGAGGTGGTGGATCC

B20 V_H nucleic acid sequence

(SEQ ID NO: 74)

Gagggtcagctggtgaggtcggcgccggcctggtcagccccggggctccctggggctgtctgcggccgctccgggttacaccttc
caacttcgacatggcctgggtcgccggccggcaagggcctgggtgtgggttccatcaccacccggcgaccacgcatct
acgcccgaactccgtgaaggccggttcaccatctccgggacaacgccaagaacacccctgtacctgcagatgaactccctgccccgag
gacaccgcgtgtactactgcgtgcggcacggctactacgacggctaccacccctgtactactggggcagggaccctggtaccctg
tcctcc

Linker-3 nucleic acid sequence

(SEQ ID NO: 75)

ggtggcggtggctcgccgggtgggtcggtggcgccggatct

B20 V_L nucleic acid sequence

(SEQ ID NO: 76)

Gacatccagatgaccagtccccctcccccgtccggcctccgtgggcgaccgggtgaccatcacctgcgggctccaggcatctcc
aactacatgtggtaccagcagaagcccccgaaggcccccaagccctgtatctactacacccatccaaactgcagtcggcgtccctcc
cggttctccggctccggctccggcaccgactacacccctgaccatctccctgcagccgaggacttcgcccacctaactactgcatggcc
agaccatctccctcacacccctggccagggcaccagctggagatcaag

IgG4 hinge nucleic acid sequence (36 nt)

(SEQ ID NO: 77)

GAGAGCAAGTACGGACC GCCCTGCCCTTGTGCCCT

IgG4 hinge amino acid sequence:

(SEQ ID NO: 78)

ESKYGPPCPPCP

CD28 TM nucleic acid sequence (84 nt)

(SEQ ID NO: 79)

ATGTTCTGGGTCTGGTGGTCGGAGGCGTGCTGGCCTGCTACAGCCTGCTGGC

ACCGTGGCCTTCATCATCTTTGGGTG

CD28 TM amino acid sequence:

(SEQ ID NO: 80)

MFWVLVVVGGVLACYSLLVTVAFIIFWV

4-1BB nucleic acid sequence

(SEQ ID NO: 81)

AAACGGGGCAGAAAGAAA ACTCCTGTATATATTCAAACAACCATTATGAGACCA GT

ACAAACTACTCAAGAGGAAGATGGCTGTAGCTGCCGATTCCAGAAGAAGAAGAAG

GAGGATGTGAACTG

CD3z nucleic acid sequence

(SEQ ID NO: 82)

CGGGTGAAAGTTAGCAGCAGAACGCCGACGCCCTGCCTACCAGCAGGCCAGAATCA

GCTGTACAACGAGCTGAACCTGGCAGAAGGGAAAGAGTACGACGTCTGGATAAGC

GGAGAGGCCGGACCTGAGATGGGGGCAAGCCTCGGCGGAAGAACCCCCAGGA

AGGCCTGTATAACGAACTGCAGAAAGACAAGATGGCCGAGGCCCTACAGCGAGATCG

GCATGAAGGGCGAGCGGAGGGGGCAAGGGCACGACGCCCTGTATCAGGGCCT

GTCCACCGCCACCAAGGATA CCTACGACGCCCTGCACATGCAGGCCCTGCCCTAA

GG

TOB1 nucleic acid sequence (2130 nt)

(SEQ ID NO: 83)

ATGGCCTTACCA GTGACCGCCTTGCTCCTGCCGCTGGCCTTGCTGCTCCACGCC

AGGCCGGAAATTGTGTTGACACAGTCTCCAGCCACCCCTGTCTTGCTCCAGGGAA

AGAGCCACCCTCTCCGCAGGGCCAGTCAGAGTGTAGCAGCTACTTAGCCTGGTAC

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CAACAGAAACCTGGCCAGGCTCCAGGCTCATCTATGATGCATCCAACAGGGC
CACTGGCATCCCAGGCCAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCAC
CATCAGCAGCCTAGAGCCTGAAGATTTCAGTTTACTGTCAGCAGCGTAGCAA
CTGGCCGATCACCTTCGGCCAAGGGACACGACTGGAGATTAAAGGCAGTAGCG
GTGGTGCTCCGGGGCGGTTCCGGTGGGGCGGCAGCAGCGAAGTGCAGCTGGT
GAGTCTGGGGAGGCTGGTACAGCCTGGCAGGTCCCTGAGACTCTCTGTGCAGCC
TCTGGATTCACCTTAATGATTATGCCATGCACTGGGTCCGCAAGCTCCAGGGAAAG
GGCCTGGAGTGGGTCTCAACTATTAGTGGAAATAGTGGTCCATAGGCTATGCGGAC
TCTGTGAAGGGCGATTCACCATCTCCAGAGACAACGCCAAGAAGTCCCTGTATCTG
CAAATGAACAGTCTGAGAGCTGAGGACACGGCTTGTATTACTGTGAAAAGATAT
ACAGTACGGCAACTACTACTACGGTATGGACGTCTGGGGCAAGGGACCACGGTCA
CCGTCCTCAGGAGGTGGATCCgaggtgcagctggagtcggcgccgtggcagccccgg
ctccctcgccgtcctcgccgcctccggctcaccttcccaacttcgacatggccctgggt
tgccgtggccaggccatctccgggacaacggccaa
gaacaccctgtacctgcagatgaaactccctgccccccgaggacaccggcgtgtactact
gcgtgcggcacggctactacgacggctacc
acctgttcgactactggggccagggcacccctggtgaccgtgtccctccgtggccgtgg
ctggccgtggtggtcggtggccggccatctccgggacaacggccaa
tctgacatccagatgaccctgaccatccccttccctgtccgcctccgtggccgggtgaccat
cacctgcggccctccgggcatct
ccaaactactgaacttgtaccagcagaagcccccaaggccccatctactacac
cttccaaacctgcagtccggcgtgcct
cccggttccggctccggctccggcaccgactacaccctgaccatctccctgcagcccc
gaggacttcggccacctaactactgcatgg
ccagaccatctccctacacccctggccaggccaccaagctggagatcaaggAGAGCAAGTACGGACCGCCCTG
CCCCCTGCCATGTTCTGGGTCTGGTGGTGGTGGTGGAGGGTGTGGCTGCCATGCTA
CACCTGCTGGTACCGTGGCTTCATCATCTTGGTGAACGGGGCAGAAAGAA
ACTCCTGTATATATTCAAAACACCATTATGAGACCAGTACAAACTACTCAAGAGGA
AGATGGCTGTAGCTGCCATTCCAGAAGAAGAAGAAGGAGGATGTGAACGTGGG
TGAAGTTCAAGCAGAGCAGCGCCAGCAGCCCTGCCTACAGCAGGCCAGAACGCTG
TACAACGAGCTGAACCTGGCAGAAGGGAGAGTACGACGTCTGGATAAGCGGA
GAGGCCGGACCCCTGAGATGGCGGCAAGCCTGGCGGAAGAACCCCCAGGAAGG
CCTGTATAACGAACTGCAGAAAGACAAGATGGCGAGGCCTACAGCGAGATCGGCA
TGAAGGGCGAGCGGAGGGGGCAAGGCCACGACGGCCTGTATCAGGGCTGTCC
ACCGCCACCAAGGATAACCTACGACGCCCTGCACATGCAGGCCCTGCCCCCAAGGTA
A

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TOB1 amino acid sequence:

(SEQ ID NO: 84)

```

MALPVTALLPLALLLHAARPEIQLTQSPATLSLSPGERATLSCRASQSVSSLYAWY
QQKPGQAPRLLIYDASN RATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSN
WPITFGQGTRLEIKGSTSGGGGGGGGGGGSEVQLVESGGLVQPGRSLRLSCAA
SGFTFNDYAMHWVRQAPGKGLEWVSTISWNSSIGYADSVKGRFTISRDNAKKSL
YLQMNSLRAEDTALYYCAKDIQYGNYYYGMDVWGQGTTVTSSGGGSEVQLVE
SGGGGLVQPGGSRLSCAASGFTFSNFDMAWVRQAPGKGLVWVSSITTGADHAIYA
DSVKGRFTISRDNAKNTLYLQMNSLRAEDTAVYYCVRHGYYDGYHLFDYWGQGT

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LTVSSGGGGGGGGGGGGSDIQMTQSPSSLASVGDRVITCRASQGISNYLNW
 YQQKPGKAPKPLIYYTSNLQSGVPSRFSGSGSGTDYTLTISSLQPEDFATYYCMQQT
 ISSYTFGQGTKEIKEKYGPPCPCPMFVVLVVVGGVLACYSLLVTVAIFIIFWVKR
 GRKKLLYIFKQPFMRPVOTTQEEEDGCSCRFPEEESEGCELRVKFSRSADAPAYQQ
 GQNQLYNELNLRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMA
 EAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR

TN-OF-B20-2 (TOB2)
 CD8a SP nucleic acid sequence

(SEQ ID NO: 85)

ATGGCCTTACCATGACCGCCTGCTCCCTGCCGCTGGCCTTGCTGCTCCACGCCGCC

AGGCCG

OF V_L nucleic acid sequence

(SEQ ID NO: 86)

GAAATTGTGTTGACACAGTCTCCAGCCACCCCTGTCTTGCTCCAGGGAAAGAGCC
 ACCCTCTCCTGCAGGGCCAGTCAGAGTGTAGCAGCTACTTAGCCTGGTACCAAACAG
 AACACCTGGCCAGGCTCCAGGCTCCTCATCTATGATGCATCCAACAGGGCCACTGGC
 ATCCCAGGCCAGGTTCACTGGCAGTGGGCTGGGACAGACTTCACTCTCACCATCAGC
 AGCCTAGAGCCTGAAGATTTCAGTTTATTACTGTCAGCAGCGTAGCAACTGGCCG
 ATCACCTCGGCAAGGGACACGACTGGAGATAAAA

Linker-1 nucleic acid sequence

(SEQ ID NO: 87)

GGCAGTACTAGCGGTGGTGGCTCCGGGGCGGTCCGGTGGGGCGGCAGCAGC

OF V_H nucleic acid sequence

(SEQ ID NO: 88)

GAAGTGCAGCTGGTGGAGTCTGGGGAGGCTGGTACAGCCTGGCAGGTCCCTGAG
 ACTCTCCTGTGCAGCCTCTGGATTACCTTAATGATTATGCCATGCACTGGTCCGG
 CAAGCTCCAGGGCAAGGGCTGGAGTGGGTCTCAACTATTAGTTGGAATAGTGGTCC
 ATAGGCTATGCGGACTCTGTGAAGGGCGATTCACCATCTCCAGAGACAACGCCAA
 GAAGTCCTGTATCTGCAAATGAACAGTCTGAGAGGCTGAGGACACGGCCTGTATT
 CTGTGCAAAAGATAACAGTACGGCAACTACTACGGTATGGACGTCTGGGGCC
 AAGGGACCACGGTCACCGTCTCCTCA

Linker-2 nucleic acid sequence

(SEQ ID NO: 89)

GGAGGTGGTGGATCC

B20 V_L nucleic acid sequence

(SEQ ID NO: 90)

Gacatccagatgaccagtcccccttccctgtccgcctccgtggcgaccatcacctgcggccctccaggcatctcc
 aactacctgaactggtaaccagcagaagcccccaaggccccctgatctactacacctccaaacctgcagtccggcgtgccctcc
 cgggtctccggctccggctccggcaccgactacacctgtaccatctccctgcagccccaggacttcgcccactactgtcatgggcc
 agaccatctccctacaccttcggccaggccaccaagctggagatcaag

Linker-3 nucleic acid sequence

(SEQ ID NO: 91)

ggtgccggcggctcggccgggtgggtcggtggccggatct

B20 V_H nucleic acid sequence

(SEQ ID NO: 92)

Gaggtgcagctggtaaccgtccggccggctggcagccccggctccctgcggctgtctgcggccctccggcttacaccttc

caacttcgacatggcctgggtgcggcaggccccggcaaggccctggtgtgggtctccatcaccaccggccgaccacgcacatct

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agggtggcggtggctgggcggtggtgggtcggtggcgccggatctgaggtgcagctggtgagtcggcgccggcgttgcacccggcaagg
ccggcggtccctgcggctgtctgcgcgectccggcttacaccttctccaacttcgacatggcctggtgccggcaggccccggcaagg
gcctgggtgggtgtctccataccacccggccgaccacccatctacgcgactccgtgaaggccggttcacatctcccgaa
acgccaagaacacccctgtacctgcagatgaactccctgcggccgaggacacccgcgtgtactactgcgtgcggcactggctactacgac
ggctaccacccgttgcactactggggcaggccacccctggtgaccgtgtctccGAGAGCAAGTACGGACC GCCCT
GCCCCCTTGCCCATGTTCTGGGTGCTGGTGGTGGTCGGAGGC GTGCTGGCCTGCT
ACAGCCTGCTGGTCACCGTGGCCTCATCATCTTGGTGAACAGGGCAGAAAGA
AACTCCTGTATATATTCAAACAACCATTATGAGACCAGTACAAACTACTCAAGAGG
AAAGATGGCTGTAGCTGCCGATTCCAGAAGAAGAAGAGGAGATGTGAAGTGC
GTGAAGTT CAGCAGAACGC CGACGCCCTGCCCTACAGCAGGGCAGAATCAGCT
GTACAAACGAGCTGAACCTGGG CAGAAGGG AAGAGTACGACGT CCTGGATAAGCGG
AGAGGCCGGGACCCCTGAGATGGGGCAAGCCTCGCCGGAAAGAACCCCCAGGAAG
GCCGTATAACGAACTGCAGAAAGACAAGATGGCCAGGGCTACAGCAGATCGGC
ATGAAGGGCGAGCGGAGGC GGCAAGGGCACGACGCCCTGTATCAGGGCCTGT
CCACCGCCACCAAGGATA CCTACGACGCCCTGCACATGCAGGCCCTGCCCTAAGG
TAA

```

TOB2 amino acid sequence:

(SEQ ID NO: 98)

```

MALPV TALLPL ALLLHAARPEIVLTQSPATLS LSPGERATLSCRAS QSVSSYLAWY
QKPGQAPRLLIYDASN RATGIPARFSGSGSGTDFTLTISSL EPEDFAVYYCQQRSN
WPITFGQQTRLEIKGSTSGGGGGGGGGSSEVQLVESGGGLVQPGRSIRLSCAA
SGFTFNDYAMHWVRQAPGKGLEWVSTISWNNSIGYADSVKGRFTISRDNAKKSL
YLMNSLRAEDTALYYCAKDIQYGNYYGMDVWGQTTVTVSSGGGSDIQMTQ
SPSSLSASVGDRVTITCRASQGISNYLNWYQQKPGKAPKPLIYYTSNLQSGVPSRFSG
SGSGTDYTLTISSLQPEDFATYYCMGQTISSYTFGQGKTLEIKGGGGGGGGGGGG
GSEVQLVESGGGLVQPGSRLSCAASGFTFSNFDMAWVRQAPGKGLVWVSSITT
GADHAIYADSVKGRFTISRDNAKNTLYLQMN SLRAEDTAVYYCVRHGYYDGYHLF
DYWGQGTLTVSSSESKYGP PCPPCPMFWLVVVGGVLACYSLLVTA VAFII FWVKR
GRKKLLYIFKQP FMRPVQTTQEDGCS CRFPEEEEGGCELRVKFSRSADAPAYQQ
GQNQLYNELNLRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNE LQKDKMA
EAYSEIGMKGERRGKGHDGLYQGLSTATKDTYDALHMQALPPR

```

TN-OF-B20-3 (TOB3)

CD8a SP nucleic acid sequence

(SEQ ID NO: 99)

```

ATGGCCTTACCA GTGACCGCCTGCT CCTGCCGTGGCCTTGCTGCTCCACGCC
AGCCG

```

OF V_H nucleic acid sequence

(SEQ ID NO: 100)

```

GAAGTG CAGCTGGTGGAGTCTGGGGAGGCTGGTACAGCCTGGCAGGTCCCTGAG
ACTCTCTGTGCAGCCTCTGGATTCACCTTAATGATTATGCCATGC ACTGGTCCGG
CAAGCTCCAGGGAAAGGGCCTGGAGTGGGTCTCAACTATTAGTTGGAATAGTGGTTCC
ATAGGCTATGCGGACTCTGTGAAGGGCGATTCACCATCTCCAGAGACAACGCCAA
GAAGTCCCTGTATCTGCAAATGAACAGTCTGAGAGCTGAGGACACGCCCTGTATTA

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CTGTGCAAAAGATATACTACAGTACGGCAACTACTACTACGGTATGGACGTCTGGGCC
 AAGGGACCACGGTCACCGTCTCCTCA
 Linker-1 nucleic acid sequence (SEQ ID NO: 101)
 GGCAGTACTAGCGGTGGTGGCTCCGGGGCGGTTCCGGTGGGGCGGCAGCAGC
 OF V_L nucleic acid sequence (SEQ ID NO: 102)
 GAAATTGTTGACACAGTCTCAGGCCACCCCTGTCTTGTCAGCTCCAGGGAAAGAGCC
 ACCCTCTCCTGCAGGGCCAGTCAGAGTGTAGCAGCTACTTAGCCTGGTACCAACAG
 AACCTGGCCAGGCTCCAGGCTCATCTATGATGCATCCAACAGGGCCACTGGC
 ATCCCAGGCCAGGTTCACTGGCAGTGGGCTGGGACAGACTCACTCTCACCATCAGC
 AGCCTAGAGCCTGAAGATTTGCAGTTATTACTGTCAAGCAGCGTAGCAACTGGCG
 ATCACCTCGGCAAGGGACACGACTGGAGATTA
 Linker-2 nucleic acid sequence (SEQ ID NO: 103)
 GGAGGTGGTGGATCC
 B20 V_L nucleic acid sequence (SEQ ID NO: 104)
 Gacatccagatgaccaggccccctcccccgtccgcctccgtggcgaccatcacctgcccggcctcccgatcc
 aactacctgaactggtaccagcagaagccggcaaggccccaaagccctgatctactacacctccaacctgcagtccggcgtgccc
 cggttctccggccggctccggcaccgactacacctgaccatctccctgcagcccaggacttcgcccacctactactgcattggcc
 agaccatctccctcacaccttggccagggcaccaagctggagatcaag
 Linker-3 nucleic acid sequence (SEQ ID NO: 105)
 ggtggcggtggctcgccgggtggctgggtggatct
 B20 V_H nucleic acid sequence (SEQ ID NO: 106)
 Gagggtcagctggtgagtcggcgccggctggtcagccccgggtccctgggtgtctgcggccatccgggtcaccttc
 caacctcgacatggcctgggtcgcccgaggccccggcaaggccctgggtgggtcccatcaccacccggccgaccacgc
 acggccgactccgtgaagggccggttaccatctccgggacaacgccaagaacacctgtacactgcagatgaactccctgcggcc
 gagaccggccgtactactgcgtgcggcacggctactacgacggctaccacctgttgcactactggggccagggcacccctgg
 taccgttc
 hinge nucleic acid sequence (SEQ ID NO: 107)
 GAGAGCAAGTACGGACGCCCTGCCCTTGCCT
 CD28 TM nucleic acid sequence (SEQ ID NO: 108)
 ATGTTCTGGGTGCTGGTGGTGGTCGGAGGGCGCTGGCTACAGCCTGCTGGTC
 ACCGTGGCCTTCATCATCTTGGGTG
 4-1BB nucleic acid sequence (SEQ ID NO: 109)
 AACACGGGGCAGAAAAGAAACTCCTGTATATATTCAAACAACCATTATGAGACCA
 ACAAAACTACTCAAGAGGAAGATGGCTGTAGCTGCCATTCCAGAAGAAGAAG
 GAGGATGTGAAC
 CD3z nucleic acid sequence (SEQ ID NO: 110)
 CGGGTGAAGTTCAGCAGAACGCCGACGCCCTGCCTACAGCAGGGCCAGAATCA
 GCTGTACAACGAGCTGAACCTGGGAGAAGGGAAAGAGTACGACGTCTGGATAAGC
 GGAGAGGCCGGACCCCTGAGATGGCGGCAAGCCTCGGCGGAAGAACCCCCAGGA

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AGGCCCTGTATAACGAACTGCAGAAAGACAAGATGGCCGAGGCCTACAGCAGAGATCG
GCATGAAGGGCGAGCGGAGGCAGGGCAAGGGCCACGACGGCTGTATCAGGGCT
GTCCACCGCCACCAAGGATACTACGACGCCCTGCACATGCAGGCCCTGCCCCCAA
GG

TOB3 nucleic acid sequence (2130 nt)

(SEQ ID NO: 111)

ATGCCCTTACCAAGTGACGCCCTGCTCCTGCCGCTGGCCTTGCTGCTCCACGCC
AGGCCGGAAGTGAGCTGGGGAGGCTGGTACAGCCTGGCAGGTC
CCTGAGACTCTCCTGTGCAGCCTGGATTACACCTTAATGATTATGCCATGCACGG
GTCCGGCAAGCTCCAGGGAAAGGGCTGGAGTGGGCTCAACTATTAGTTGAAATAG
TGGTCCATAGGCTATGCCACTCTGTGAAGGGCGATTCAACCATCTCCAGAGACAA
CGCCAAGAAGTCCCTGTATCTGCAAATGAACAGCTGAGAGCTGAGGACACGGCCT
TGTATTACTGTGCAAAAGATAACAGTACGGCAACTACTACTACGGTATGGACGT
GGGGCCAAGGGACCACGGTACCGTCTCCTCAGGCAGTACTAGCGGTGGCTCC
GGGGCGGGTCCGGTGGGGCGGCAGCAGCAGAAATTGTTGACACAGTCTCCAGC
CACCTGTCTTGCTCCAGGGAAAGAGCCACCCCTCCTGCAGGGCAGTCAGAG
TGTAGCAGCTACTTAGCTGGTACCAACAGAAACCTGGCCAGGCTCCAGGCTCC
CATCTATGATGCATCCAACAGGGCACTGGCATCCCAGCCAGGTTCAGTGGCAGTG
GGTCTGGACAGACTTCACTCTCACCATCAGCAGCCTAGAGCTGAAGATTTGCAG
TTTATTACTGTGACAGCCTAGCAACTGGCGATCACCTGGCCAAGGGCACGAC
TGGAGATTAAGGAGGTGGATCCGacatccagatgaccagtcctccatcc
gaccgggtgaccatcacctgcggggcctccaggcatctcaactacctgaactgg
ccctgtactacaccccaacctgcagtccggcgtgccctccggatccggc
tccctgcagccccgaggactcgccacactactgcattggccagaccatctcc
agggtgtgggtggctcggcgggtggatccggatccggatctgagg
ccggcggctccctgcggcgtgtccgcgcgcctccggatcc
gcctgggtgggtgtccatcaccacccggcgcaccacgc
acgccaagaacacccctgtactgcagatgaaactcc
ggctaccacccctgttcactacttggccaggcaccctggatcc
GAGA
GCCCCCCTGCCCTATGTTCTGGGTGCTGGTGGTGGCGTGGCTGGCTGCT
ACAGCCTGCTGGTACCGTGGCCTCATCATCTTGTTGGTGAACGGGCAGAAAGA
AACTCCTGTATATATCAACAAACCATTTATGAGACCAGTACAAACTACTCAAGAGG
AAAGATGGCTGTAGCTGCCGATTCAGAAGAAGAAGAAGAAGGAGGATGTAACTGCC
GTGAAGTTCAGCAGAAGGCCGACGCCCTGCCCTACACAGCAGGGCCAGAAC
GTACAAACGAGCTGAACCTGGCAGAAGGGAAAGAGTACGACGTCCTGGATAAGCG
AGAGGCCGGGACCCCTGAGATGGCGGCAAGCCTCGGCGAAGAACCCCCAGGAAG
GCCTGTATAACGAACCTGCAGAAAGACAAGATGGCCGAGGCCTACAGCAG
ATGAAGGGCAGCGGAGGGGGCAAGGGCCACGACGGCTGTATCAGGGCTG
CCACCGCCACCAAGGATAACCTACGACGCCCTGCACATGCAGGCCCTGCC
TAA

-continued

TOB3 amino acid sequence:

MALPVTLALLPLALLLHAARPEVQLVESGGGLVQPGRSRLSLSCAASGFTFNDYAM
 HWVRQAPGKGLEWVSTISWNSGSIGYADSVKGRFTISRDNAKKSLYLQMNSLRAE
 DTALYYCAKDIQYGNYYYGMDVWGQGTTVTVSSGSTSAGGSAGGSAGGSSEIVL
 TQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPAR
 FSGSGSGTDFTLISSLEPEDFAVYYCQORSNWPITFGQGTRLEIKGGGSDIQMTO
 SPSSLASAVGDRVTITCRASQGISNYLNWYQQKPGKAPKPLIYYTSNLQSGVPSRFSG
 SGSGTDYTLTISSLQPEDFATYYCMGQTISSYTFGQGTTKLEIKGGGSGGGGGGG
 GSEVQLVESGGGLVQPGGSLRLSCAASGFTFSNFDMAWVRQAPGKGLVWVSSITT
 GADHAIYADSVKGRFTISRDNAKNTLYLQMNSLRAEDTAVYYCVRHGYYDGYHLF
 DYWGQGTLTVSSSESKYGPCCPMFWVLVVVGGVLACYSLLVTVAFIIFWVKR
 GRKKLLYIFKQPFMRPVQTTQEEDGCSRFPEEEEGGCRLRKFSRSADAPAYQQ
 GQNQLYNELNLGRREYDVLDKRRGRDPEMGKPRRKNPQEGLYNELQDKMA
 EAYSEIGMKGEERRRGKGDGLYQGLSTATKDTYDALHMQALPPR

(SEQ ID NO: 112)

TN-OF-B20-4 (TOB4)

CD8a SP nucleic acid sequence

(SEQ ID NO: 113)

ATGGCCTTACCATGTGACCGCCTGCTCTGCCCTGGCCTTGCTGCTCCACGCC

AGGCCG

OF V_H nucleic acid sequence

(SEQ ID NO: 114)

GAAGTCAGCTGGAGTCTGGGGAGGCTGGTACAGCTGGCAGGTCCCTGAG
 ACTCTCCTGTGAGCCTCTGGATTACCTTAATGATTATGCCATGCACTGGGTC
 CAAGCTCCAGGAAGGGCCTGGAGTGGGTCTCAACTATTAGTTGAATAGTGGT
 ATAGGCTATGCCACTCTGTGAAGGGCGATTACCATCTCCAGAGACAACGCC
 GAAGTCCTGTATCTGCAAATGAACAGTCTGAGAGCTGAGGACACGCC
 CTGTGCAAAAGATAACAGTACGGCAACTACTACTACGGTATGGACGTCTGG
 AAAGGACCACGGTCACCGTCTCCTCA

Linker-1 nucleic acid sequence

(SEQ ID NO: 115)

GGCAGTACTAGCGGTGGCTCGGGGGCGGTCCGGTGGGGCGGCAGCAGC

OF V_L nucleic acid sequence

(SEQ ID NO: 116)

GAAATTGTGTTGACACAGTCTCCAGCCACCCGTCTTGTCTCCAGGGAAAGAGC
 ACCCTCTCCTGAGGGCAGTCAGAGTGTAGCAGCTACTTAGCCTGGTACCAACAG
 AACCTGCCAGGCTCCAGGCTCTCATCTATGATGCATCCAACAGGGCACTGG
 ATCCCAGCCAGGTTCACTGGCAGTGGTCTGGGACAGACTTCACCTCACCATCAGC
 AGCCTAGAGCCTGAAGATTTGCAGTTATTACTGTCAGCAGCGTAGCAACTGG
 ATCACCTCGGCCAAGGGACACGACTGGAGATTA

Linker-2 nucleic acid sequence

(SEQ ID NO: 117)

GGAGGGTGGTGGATCC

B20 V_H nucleic acid sequence

(SEQ ID NO: 118)

Gaggtgcagctggtgagtcggcgccctggcagccccggcgctccctgccc
 tgcggctgtctgcgcgcctccgcacccatc

caacttcgacatggcctggtgccggcaggccccggcaaggccctggtgt
 cccatcaccaccggcgccaccacgcccattc

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acggccgactccgtgaaggcccggttaccatccccggacaacgccaagaacaccctgtacctgcagatgaactccctgcgggcccgg
gacaccgcgtgtactactgcgtgcggcacggctactacgacggctaccacctgttcgactactggggcagggcaccctggtgaccgtg
tcctcc

Linker-3 nucleic acid sequence

(SEQ ID NO: 119)

ggtggcggtggtcgccgggtgggtcggtggatct

B20 V_L nucleic acid sequence

(SEQ ID NO: 120)

Gacatccagatgaccagtcggctccctgtccgcctccgtggcgaccgggtgaccatcacctgcggcctcccgatctcc
aactacctgaactggtaccagcagaagcccgcaaggccccaaagccctgatctactacacccctcaacactgcagtccggcgtgc
cggttctccggccggctccggactacaccctgaccatctccctgcagccgaggacttgcacccatactgcattggcc
agaccatctccctacacccctggccagggcaccaaagctggagatcaag

hinge nucleic acid sequence

(SEQ ID NO: 121)

GAGAGCAAGTACGGACGCCCTGCCCCCTTGCCT

CD28 TM nucleic acid sequence

(SEQ ID NO: 122)

ATGTTCTGGGTGCTGGTGGTCGGAGGCGTGCTGGCTGCTACAGCCTGCTGGTC

ACCGTGGCCTTCATCATCTTGGGTG

4-1BB nucleic acid sequence

(SEQ ID NO: 123)

AAACGGGGCAGAAAAGAAACTCTGTATATATTCAAACAACCATTATGAGACCACT

ACAAACTACTCAAGAGGAAGATGGCTGTAGCTGCCATTCCAGAAGAAGAAGAAG

GAGGATGTGAACTG

CD3z nucleic acid sequence

(SEQ ID NO: 124)

CGGGTGAAGTTACGCAGAACGCCGACGCCCTGCCTACCAGCAGGCCAGAATCA

GCTGTACAACGAGCTGAACCTGGGAGAAGGGAAAGAGTACGACGTCTGGATAAGC

GGAGAGGCCGGGACCCCTGAGATGGCGCAAGCCCTCGGCGGAAGAACCCCCAGGA

AGGCCTGTATAACGAACACTGCAGAAAGACAAGATGGCGAGGCCTACAGCGAGATCG

GCATGAAGGCGAGCGAGGCGGGCAAGGCCACGACGCCCTGTATCAGGCC

GTCCACCGCCACCAAGGATACTACGACGCCCTGCACATGCAGGCCCTGCCCAA

GG

TOB4 nucleic acid sequence (2130 nt)

(SEQ ID NO: 125)

ATGGCCTTACCGTGAACGCCCTGCTCCCTGCCGCTGGCCTTGCTGCTCCACGCC

AGGCCGGAAAGTGCAGCTGGTGGAGTCTGGGGAGGCTTGGTACAGCCTGGCAGGT

CCTGAGACTCTCTGTGCAGCCTCTGGATTCACCTTAATGATTATGCCATGCACTGG

GTCCGGCAAGCTCAGGGAGGGCCTGGAGTGGGTCTCAACTATTAGTTGGAATAG

TGGTTCCATAGGCTATGCGGACTCTGTGAAGGCCGATTCAACATCTCCAGAGACAA

CGCCAAGAAGTCCACGGTACGGCAACTACTACGCTATGGACACGGC

TGTATTACTGTCAAAAGATAACAGTACGCCACTACTACGCTATGGACCGT

GGGGCCAAGGGACCACGGTACCGTCTCCCTCAGGCAGTACTAGCGGTGGTGGCTCC

GGGGCGGTTCCGGTGGGGCGCAGCAGCAGGAAATTGTGTTGACACAGTCTCCAGC

CACCCCTGTCTTGCTCCAGGGAAAGAGCCACCCCTCTCCTGCAGGGCAGTCAGAG

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TGTTAGCAGCTACTTAGCCTGGTACCAACAGAAACCTGGCCAGGCTCCCAGGCTCCT
CATCTATGATGCATCCAACAGGGCCACTGGCATCCCAGCCAGGTTAGTGGCAGTG
GGTCTGGGACAGACTTCACTCTCACCATCAGCAGCCTAGAGCTGAAGAGTTTCAG
TTTATTACTGTCAAGCAGCGTAGGCAACTGGCCGATCACCTCGGCCAAGGGACACGAC
TGGAGATTAAGGAGGTGGATCCgaggtcagctggagtccggggggcctggtgacggccggcg
gctccctgcggcgtgtccgcgcgcctccggcattcaccttcacatcgacatggcctgggtgcggcaggccccggcaagggcctgg
gtgggtgtccctccatcaccacccggcgccgaccacgcacatcactccggactcggtaagggccgggtcaccatctccggacaacgc
agaacacccctgtacctgcagatgaactccctgcggggccgaggacaccgcgtgtactactgcgtgcggcacggctactacgacggctac
caccctgtcactactggggccaggcaccctggtaccgtgtccctccggtgccgtggctccggcggtgggtgggtgggtggggcg
atctGacatccagatgacccagtcccccctccctgtccgcctccgtggcaccgggtgaccatcac
ctcccaactacctgaacttgtaccagcagaagccggcaaggccccatcactacacccctcaac
ctgcagtccggcgtgccctccgggttctccggctccggcaccgactacaccctgaccatctccctccgtcagccgaggacttc
ccggccatactgcatggccacccatctccctccggatcaagGAGAGCAAGTACGGACC
CCCCCCTTGCCCTATGTTCTGGGTGCTGGTGGTGGTCGGAGGCGTGGCTGGCCTGCTA
CAGCCTGCTGGTACCGTCACCGTGGCCTCATCATCTTGAGACCAAGTACAAACTACTCAAGAGGA
ACTCCTGTATATATTCAAACAACCATTATGAGACCAAGTACAAACTACTCAAGAGGA
AGATGGCTGTAGCTGCCGATTCAGAGAAGAAGAAGGAGGATGTGAACTGCCG
TGAAGTTCAGCAGAAGGCCGACGCCCTGCCTACCAGCAGGCCAGAACAGCTG
TACAACGAGCTGAACCTGGGAGAAGGGAGAGTACGACGCCCTGGATAAGCGGA
GAGGCCGGACCTGAGATGGCGGAAGGCTCGCGGAAGAACCCCCAGGAAGG
CTGTATAACGAACCTGCAGAAAGACAAGATGGCGAGGCCTACAGCGAGATCGGCA
TGAAGGGCGAGGGAGGGGGCAAGGCCACGACGCCCTGTATCAGGCCCTGTC
ACCGCCACCAAGGATACCTACGACGCCCTGCACATGCAGGCCCTGCCCAAGGTA
```

A

TOB4 amino acid sequence:

(SEQ ID NO: 126)

```
MALPVTALLPLALLHAARPEVQLVESGGGLVQPGRSRLSLSCAASGFTFNDYAM
HWVRQAPGKGLEWVSTISWNSGSIGYADSVKGRFTISRDNAKSLYLMQNSLRAE
DTALYYCAKDIQYGNYYGMDVWGQGTTTVSSGSTSGGSGGSGGGSSSEIVL
TQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPAR
FSGSGSGTDFTLTISLEPEDFAVYYCQQRSNWPITFGQGTRLEIKGGGSEVQLVE
SGGLVQPGGSLRLSCAASGFTFSNFDMAWVRQAPGKGLVVVSSITTGADHAIYA
DSVKGRFTISRDNAKNTLYLQMNSLRAEDTAVYYCVRHGYYDGYHLFDYWGQGT
LTVTSSGGGGGGGGGGSDIQMTQSPSSLASVGDRVTITCRASQGISNYLNW
YQQKPGKAPKPLIYYTSNLQSGVPSRFSGSGSGTDYTLTISLQPEDFATYYCMQQT
ISSYTFQGQGTKLEIKEKYGPFCPPCPMFVWLVVVGGVLACYSLTVAFIIFWVKR
GRKKLLYIFKQPFMRPVOTTQEEDGCSRFPEEEEGGCELRVKFSRSADAPAYQQ
GQNQLYNELNLGRREEEYDVLDKRRGRDPEMGKPRRKNPQEGLYNELQDKM
EAYSEIGMKGERRRGKGDGLYQGLSTATKDTYDALHMQALPPR
```

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OF-V _H -CDR1 :	(SEQ ID NO: 127)
NDYAMH	
OF-V _H -CDR2 :	(SEQ ID NO: 128)
TISWNNSGSIGYADSVKG	
OF-V _H -CDR3 :	(SEQ ID NO: 129)
DIQYGNYYYYGMDV	
OF-V _L -CDR1 :	(SEQ ID NO: 130)
RASQSVSSYLA	
OF-V _L -CDR2 :	(SEQ ID NO: 131)
DASNRAT	
OF-V _L -CDR3 :	(SEQ ID NO: 132)
QQRSNWPIT	

BCMA-20 V_L

Region	Sequence Fragment	Residues of SEQ ID No: 12	Length	SEQ ID No:
LFR1	DIQMTQSPSSLSASVGDRVTITC	1-23	23	SEQ ID No: 133
CDR-L1	RASQGISNYLN	24-34	11	SEQ ID No: 134
LFR2	WYQQKPGKAKPPLIY	35-49	15	SEQ ID No: 135
CDR-L2	YTSNLQS	50-56	7	SEQ ID No: 136
LFR3	GVPSRFSGSGSGTDYTLTISSLQPEDFATYYC	57-88	32	SEQ ID No: 137
CDR-L3	MGQTISSYT	89-97	9	SEQ ID No: 138
LFR4	FGQGTKLEIK	98-107	10	SEQ ID No: 139

BCMA-20V_H

Region	Sequence Fragment	Residues of SEQ ID No: 16	Length	SEQ ID No:
HFR1	EVQLVESGGGLVQPGGSLRLSCAASGFTFS	1-30	30	SEQ ID No: 140
CDR-H1	NFDMA	31-35	5	SEQ ID No: 141
HFR2	WVRQAPGKGLVWVS	36-49	14	SEQ ID No: 142
CDR-H2	SITTGADHAIYADSVKG	50-66	17	SEQ ID No: 143
HFR3	RFTISRDNAKNTLYLQMNSLRAEDTAVYYCVR	67-98	32	SEQ ID No: 144
CDR-H3	HGYYDGYHLFDY	99-110	12	SEQ ID No: 145

-continued

Region	Sequence	Fragment	Residues of SEQ ID No: 16	SEQ Length	ID No:
HFR4	WGQGTLVTVSS		111-121	11	SEQ ID No: 146

[0274] The scope of the present invention is not limited by what has been specifically shown and described hereinabove. Those skilled in the art will recognize that there are suitable alternatives to the depicted examples of materials, configurations, constructions and dimensions. Numerous references, including patents and various publications, are cited and discussed in the description of this invention. The citation and discussion of such references is provided merely to clarify the description of the present invention and is not an admission that any reference is prior art to the invention described herein. All references cited and discussed in this

specification are incorporated herein by reference in their entirety. Variations, modifications and other implementations of what is described herein will occur to those of ordinary skill in the art without departing from the spirit and scope of the invention. While certain embodiments of the present invention have been shown and described, it will be obvious to those skilled in the art that changes and modifications may be made without departing from the spirit and scope of the invention. The matter set forth in the foregoing description and accompanying drawings is offered by way of illustration only and not as a limitation.

SEQUENCE LISTING

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Sequence total quantity: 146
SEQ ID NO: 1      moltype = DNA length = 63
FEATURE           Location/Qualifiers
source            1..63
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 1
atggcattac cagtgaccgc cttgcttcgt ccgctggct tgctgttcca cgccggcagg 60
ccg                               63

SEQ ID NO: 2      moltype = AA length = 21
FEATURE           Location/Qualifiers
source            1..21
mol_type = protein
organism = synthetic construct

SEQUENCE: 2
MALPVTLALL PLALLLHAAR P                                21

SEQ ID NO: 3      moltype = DNA length = 321
FEATURE           Location/Qualifiers
source            1..321
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 3
gaaatttgtt tgacacagtc tccagccacc ctgtctttgt ctccaggggaa aagagccacc 60
ctctcttgca gggccaggctc gagtgttagc agctacttag cctggtagcca acagaaacct 120
ggccaggctc ccaggcttcatgttcatatggat gcataccaaa gggccactgg catcccgacc 180
aggttcagtc gcaatgggtt tggggacagac ttcaacttcca ccatacggcag ctttagggct 240
gaagattttt cagtttattta ctgttcagcag cgttagcaact ggccgatcac ctccggccaa 300
gggacacgac tggagattaa a                                321

SEQ ID NO: 4      moltype = AA length = 107
FEATURE           Location/Qualifiers
source            1..107
mol_type = protein
organism = synthetic construct

SEQUENCE: 4
EIVLVTSPAT LSLSPGERAT LSCRASQSVS SYLAWYQQKP GQAPRLLIYD ASN RATGIPA 60
RFSGSGSGSTD FTLTISSLEP EDFAVYYCQQ RSNWPITFGQ GTRLEIK                                107

SEQ ID NO: 5      moltype = DNA length = 54
FEATURE           Location/Qualifiers
source            1..54
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 5
ggcagtacta gcggtgggtgg ctccgggggc ggttccggtg gggggggcag cagc                                54

SEQ ID NO: 6      moltype = AA length = 18

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FEATURE	Location/Qualifiers
source	1..18
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 6	
GSTSGGGGGG GSBBBBBB	18
SEQ ID NO: 7	moltype = DNA length = 366
FEATURE	Location/Qualifiers
source	1..366
	mol_type = other DNA
	organism = synthetic construct
SEQUENCE: 7	
gaagtgcagc ttgtggagtc tgggggaggc ttgttacagc ctggcaggc cctgagactc 60	
tccctgtcag cctctggatt cacccatata gattatgcca tgcaactgggt ccggcaagct 120	
ccacggaaagg qcctggagtg ggcttcaact attatgttgc atagtgttc cataggctat 180	
gcccactctg tgaaggggcg attcaccatc tccagagaca acgccaagaa gtccctgtat 240	
ctgcaaatgta acagtcttag agctgaggac acggccttgtt attactgtgc aaaagatata 300	
cgttacggca actactacta cggtatggac gtctggggcc aaggggaccac ggtcacccgtc 360	
tcctca	366
SEQ ID NO: 8	moltype = AA length = 122
FEATURE	Location/Qualifiers
source	1..122
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 8	
EVQLVESGGVQPGKGRFTI LVQPGRLRL SCAASGFTFN DYAMHWVRQAPGKGLEWVST ISWNNSGSIGY 60	
ADSVKGRFTI SRDNAAKSLY LQMNSLRAED TALYYCAKDI QYGNYYYYGMD VWGQGTTVTV 120	
SS	122
SEQ ID NO: 9	moltype = DNA length = 15
FEATURE	Location/Qualifiers
source	1..15
	mol_type = other DNA
	organism = synthetic construct
SEQUENCE: 9	
ggaggtggtg gatcc	15
SEQ ID NO: 10	moltype = AA length = 5
FEATURE	Location/Qualifiers
source	1..5
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 10	
GGGGS	5
SEQ ID NO: 11	moltype = DNA length = 321
FEATURE	Location/Qualifiers
source	1..321
	mol_type = other DNA
	organism = synthetic construct
SEQUENCE: 11	
gacatccaga tgacccagtc cccctcttcc ctgtccgcct ccgtgggcga ccgggtgacc 60	
atcacctgcc gggcatccccca gggcatcttca aactacctga actggatccca gcagaaggccc 120	
ggcaaggccc ccaagccccct gatctactac acctccaaacc tgcaactggg cgtgcctcc 180	
cggttctccg gtcctggctc cggcaccgac tacacccatca ccatctccctc cttcgccccc 240	
gaggacttcg ccacctaacta ctgcattggc cagaccatct cctcttacac cttcgcccg 300	
ggcaccacggc tggatcaa g	321
SEQ ID NO: 12	moltype = AA length = 107
FEATURE	Location/Qualifiers
source	1..107
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 12	
DIQMTQSPSS LSASVGDRVT ITCRASQGIS NYLNWYQQKP GKAPKPLIYY TSNLQSGVPS 60	
RFSGSGSGTD YTLTISSLQP EDFATYYCMG QTISSYTFQG GTKLEIK	107
SEQ ID NO: 13	moltype = DNA length = 45
FEATURE	Location/Qualifiers
source	1..45
	mol_type = other DNA
	organism = synthetic construct
SEQUENCE: 13	
ggtggcggtg gtcggggcg tggtgggtcg ggtggcgccg gatct	45

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SEQ ID NO: 14      moltype = AA  length = 15
FEATURE
source
1..15
mol_type = protein
organism = synthetic construct
SEQUENCE: 14
GGGGSGGGGS GGGGS                                         15

SEQ ID NO: 15      moltype = DNA  length = 363
FEATURE
source
1..363
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 15
gagggtgcagc tgggtggagtc cggcgccgc ctgggtgcagc cccggggctc cctgcggctg  60
tccctgcgcg cctccggctt caccttctcc aacttcgacca tggcctgggt gccgcaggcc 120
cccccgcgaagg gctgtgtgtt ggtgtctcc atcaccaccc gccgcgacca cgccatctac 180
gccccactccg tgaaggggccg gttcaccatc tcccgggacca acggccaaaga caccctgtac 240
ctgcagatgca atccctctcg ggcgcaggac accggcgtgt actactgcgt gccgcacggc 300
tactacgacg gtcaccacct gttcgactac tggggccagg gcacctgtgtt gaccgtgtcc 360
tcc                                         363

SEQ ID NO: 16      moltype = AA  length = 121
FEATURE
source
1..121
mol_type = protein
organism = synthetic construct
SEQUENCE: 16
EVQLVESGGG LVQPGGSLRL SCAASGFTPS NFDMAWRQA PGKGLVWVSS ITTGADHAIY  60
ADSVKGRFTI SRDNNAKNTLY LQMNSLRAED TAVYYCVRHG YYDGYHLFDY WGQGTLVTVS 120
S                                         121

SEQ ID NO: 17      moltype = DNA  length = 165
FEATURE
source
1..165
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 17
ttcgtgcggg tcttcctgccc agcgaagccc accacgacgc cagcgcggcg accaccaaca 60
cccgccgcaca ccatacgcgcc gcaagccctgt tccctgcgcg cagaggcggtt ccggccagcg 120
gcggggggcgc cagtgcacac gagggggctg gacttcgcct gtgtat                                         165

SEQ ID NO: 18      moltype = AA  length = 55
FEATURE
source
1..55
mol_type = protein
organism = synthetic construct
SEQUENCE: 18
FVPVFLPAKP TTTPAPRPPT PAPTIASQPL SLRPEACRPA AGGAHVTRGL DFACD      55

SEQ ID NO: 19      moltype = DNA  length = 72
FEATURE
source
1..72
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 19
atctacatct gggcgccctt ggccggact tgggggttcc ttctccgtc actggttatc  60
accctttact gc                                         72

SEQ ID NO: 20      moltype = AA  length = 24
FEATURE
source
1..24
mol_type = protein
organism = synthetic construct
SEQUENCE: 20
IYIWAPLAGT CGVLLLSLVI TLYC                                         24

SEQ ID NO: 21      moltype = DNA  length = 126
FEATURE
source
1..126
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 21
aaacggggca gaaagaaaact cctgttatata ttcaaacaac catttatgag accagtacaa 60
actactcaag aggaagatgg ctgttagctgc cgattccag aagaagaaga aggaggatgt 120

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gaactg		126
SEQ ID NO: 22	moltype = AA length = 42	
FEATURE	Location/Qualifiers	
source	1..42	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 22		
KRGRKKLLYI FKQPFMRPVQ TTQEEDGCSC RFPEEEGGC EL		42
SEQ ID NO: 23	moltype = DNA length = 339	
FEATURE	Location/Qualifiers	
source	1..339	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 23		
agagtgaagt tcagcaggag cgcagacgcc cccgcgtacc agcagggcca gaaccagctc 60		
tataaacgacg tcaatcttagg acgaagagag gactacgatg ttggacaa gagacgtggc 120		
cgggaccctg agatgggggg aaagcgaga aggaagaacc ctcaggaaagg cctgtacaat 180		
gaactgcaga aagataaatg ggcggaggcc tacagtgaga ttggatgaa aggcgacgc 240		
cggaggggca aggggcacga tgcccttac cagggtctca gtacagccac caaggacacc 300		
tcagcagccc ttcacatgca ggccctgccc cctcgctaa 339		
SEQ ID NO: 24	moltype = AA length = 112	
FEATURE	Location/Qualifiers	
source	1..112	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 24		
RVKFSRSADA PAYQQQNQL YNELNLGRRE EYDVLDKRRG RDPEMGGKPR RKNPQEGLYN 60		
ELQKDKMAEA YSEIGMKGER RRGKGHDGLY QGLSTATKDT YDALHMQALP PR 112		
SEQ ID NO: 25	moltype = DNA length = 2250	
FEATURE	Location/Qualifiers	
source	1..2250	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 25		
atggccattac cagtgaccgc ctgtgcctg cccgtggcctg tgctgtccca cgccgcagg 60		
ccggaaattg ttttgacaca gtctccagcc accctgtctt tgctccagg gaaaagagcc 120		
acccctctct gcagggccag tcagagtgtt agcagctact tagcctgtta ccaacagaaa 180		
cctggccagg ctccccaggct cctcatctat gatgcattca acagggccac tggcatccca 240		
cccaagggtca gtggcgtgg gtctgggaca gacttcactc tcacccatcg cagccatagag 300		
cctgaagatt ttgcgttta ttactgtcg cagcgatgact actcgccgtt caccttcggc 360		
caaggggacac gactggatgat taaaggcgtg actagcggtt gtggctccgg gggcggttcc 420		
ggtgtggggcg gcaagcgcga agtgcagctg gtggagttctg gggggaggctt ggtacagcct 480		
ggcagggttcc tgagactctc ctgtgcagcc tctggatccca cctttatgaa ttatgcatg 540		
cactgggtcc ggcgaactcc agggaaaggcc tcggagttggg ttcactat tagtggaaat 600		
agtgggttca taggtatgc ggactctgtg aaggccatg tcacccatctc cagagacac 660		
gccaagaagt ccctgtatct gcaaatgaaat agtctgagat ctgaggacac ggccttgc 720		
tactgtgcaa aagatataca gtacgcgcaat tactactact gtagtggactt ctggggccaa 780		
gggaccacggg tcaccgttcc tcaggagggtt ggtggatccg acatccgat gaccggatcc 840		
ccctccccc tttccgcctc ctgtggccac ccgtggccac tcacccatcg ggcctcccg 900		
ggcatctcca actacctgaa ctggtaccag cagaagcccg gcaaggcccc caagccctcg 960		
atctactaca cttccaaacctt gcacgtccggc gtggccctccc gggttctccgg ctccggctcc 1020		
ggcaccgact acaccctgcac catctccctc ctgcacccggc aggacttgc caccctactac 1080		
tgcattggccc agaccatctc ctccatcaccc ttccggccagg gcaccaactg ggagatcaag 1140		
ggtgtgggttgc gtcggggcggtt tggtgggtcg ggtggggccg gatctgagggt gcacgtgg 1200		
gagtccggcg gggccctgggt gcacggccggc gggtcccttcgc ggctgtccctg cgccgcctcc 1260		
gggttccaccc tttccaaacctt cgacatggcc ttgggtccggc aggccccccgg caagggctcg 1320		
gtgtgggtgtt cttccatcaccc acaccggccca gaccacggcc tctacgcgca ctccgtgaag 1380		
ggccgggttca ccatctcccg ggacaaacggc aagaacaccgg ttttgcgttca gatgactcc 1440		
ctgcggggccg aggacaccgcg cgtgtactac tgcgtgcggc acggctacta cgacggctac 1500		
caacctgttgc actactgggg ccacggccggc ctgtgtaccgg ttttgcgttccctt ctgtggccgtt 1560		
tttcgttcccg cgaagccaccc caccgcgcaccc ggcggccgcac caccacacc ggcggccacc 1620		
atcgctgcgcg accccctgtc cttccgcctca gggccgttcc gcggccggcc gggggggccca 1680		
gtgcacacgca ggggggttggaa cttccgttgc gatatctaca ttgtggccgc cttggccggg 1740		
acttgtgggg ttcccttcctt gtcactgggtt atcaccctttt actgcaaaacgg gggcggaaag 1800		
aaactccgtt atatattcaa acaaccattt atgagaccatc tacaaactac tcaagggaa 1860		
gatgggttgc gtcgtccggatt tccagaagaa gaagaaggag gatgtgaact gagagtgaag 1920		
ttcagcggaga ggcggacacgc ccccgccgtac cagcaggccggc agaaccggctt ctatggcc 1980		
ctcaatcttag gacgaagaga ggagtttgc gttttggaca agagacgtgg ccggggaccc 2040		
gagatggggg gaaaggccggag aaggaagaac cctcaggaaac ggcctgtacaa tgaactgcag 2100		
aaagataaga tggcgaggac ctacagtgtatggatgaa aaggcgagccg ccggggggcc 2160		
aaggggcaccg atggcccttta ccagggtctc agtacagccca ccaaggacac ctacgcaccc 2220		
cttcacatgc agggccctgccc ccctcgctaa 2250		

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SEQ ID NO: 26      moltype = AA  length = 749
FEATURE          Location/Qualifiers
source           1..749
                 mol_type = protein
                 organism = synthetic construct
SEQUENCE: 26
MALPVTALLL PLALLLHAAR PEIVLTQSPA TLSLSPGERA TLSCRASQSV SSYLAWYQQK 60
PGQAPRLLIY DASN RATGIP ARFSGSGSGT DFTLTISSE PEDFAVYYCQ QRSNWPIFG 120
QGTRLEIKGS TSGGGSGGGS GGGGSEVOL VESGGGLVQGP GRSLRLSCAA SGFTPNDYAM 180
HWRQAPGKG LEWVSTISWN SGSIGYADSV KGRFTISRDN AKKSLYLQMN SLRAEDTALY 240
YCAKDIQYGN YYGYMDVWQG GTTIVTVESSGG GGSDIQMTQS PSSLASAVGD RVTITCRASQ 300
GISNYLNWYQ QKPGKAPKPL IYYTSNLQSG VPSRFSGSGS GTDYTLTISS LQPEDFATYY 360
CMQQTISYYT PGQGKLEIK GGGGGGGGGG GGGGSEVOLV ESGGGLVQPG GSRLRLSCAAS 420
GFTFSNFDMA WVRQAPGKGL VWVSSITTG A DHAIYADSVK GRFTISRDNA KNTLYLQMNS 480
LRAEDTAVYY CVRHGYYDGY HLFDYWGQGT LTVTVESSFPVP FLPAKPTTP APRPPTPAPT 540
IASQPLSLRP EACRPAAGGA VHTRGLDFAC DIYIWAPLAG TCGVLLLSLV ITLYCKRGRK 600
KLLYIFKQPF MRPVQTTQEE DGCSRCFPEE EEGGCERLVK FSRSADAPAY QQQQNOLYNE 660
LNLRREEYD VLDRKRRGRDP EMGGKPRRK N PQEGLYNELQ KDKMAEAYSE IGMKGERRRG 720
KGHDGLYQQL STAKDTYDA LHMQALPPR 749

SEQ ID NO: 27      moltype = DNA  length = 63
FEATURE          Location/Qualifiers
source           1..63
                 mol_type = other DNA
                 organism = synthetic construct
SEQUENCE: 27
atggcccttac cagtgaccgc cttgctcctg ccgtggcct tgctgctcca cgccgccagg 60
ccg 63

SEQ ID NO: 28      moltype = DNA  length = 366
FEATURE          Location/Qualifiers
source           1..366
                 mol_type = other DNA
                 organism = synthetic construct
SEQUENCE: 28
gaagtgcagc tggggggagtc tggggggaggo ttggtagcagc ctggcagggtc cctgagactc 60
tcctgtcgag cctctggatt caccttaat gattatgc ca tgcaactgggt ccggcaagct 120
ccaggaaagg goctggagtg ggtctcaactt attagttggaa atagttggtc cataggctat 180
gcccggactc tgaaggggccg attccatc tccagagaca acggcaagaa gtccctgtat 240
ctgcaaatatg acagttctgag agctggggac acggccctgtt attactgtgc aaaatata 300
cagtacggca actactacta cggtatggac gtctggggcc aaggggaccac ggtcacggc 360
tcctca 366

SEQ ID NO: 29      moltype = DNA  length = 54
FEATURE          Location/Qualifiers
source           1..54
                 mol_type = other DNA
                 organism = synthetic construct
SEQUENCE: 29
ggcgtacta gcggtggtgg ctccgggggc ggttccggtg gggggggcag cagc 54

SEQ ID NO: 30      moltype = DNA  length = 321
FEATURE          Location/Qualifiers
source           1..321
                 mol_type = other DNA
                 organism = synthetic construct
SEQUENCE: 30
gaaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccaggggg aagagccacc 60
ctctcctgcgca gggccgtca gagttttagc agtactttag cttgttacca acagaaacct 120
ggccagggttc ccagggtctt catctatg gcatccaaacca gggccactgg catcccgacc 180
aggttcgtg cgttgtggtc tgggacagac ttcaactctca ccatcagcag cctagagct 240
gaagattttgc agtttattt ctgtcagcag cgttagcaact ggccgatcac cttccggccaa 300
ggacacacgac tggagattaa a 321

SEQ ID NO: 31      moltype = DNA  length = 15
FEATURE          Location/Qualifiers
source           1..15
                 mol_type = other DNA
                 organism = synthetic construct
SEQUENCE: 31
ggaggtggtg gatcc 15

SEQ ID NO: 32      moltype = DNA  length = 321
FEATURE          Location/Qualifiers
source           1..321

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mol_type = other DNA
organism = synthetic construct

SEQUENCE: 32
gacatccaga tgaccaggc cccctcctcc ctgtccgcct ccgtggcgca cggggtgacc 60
atcacctgcc gggcctccca gggcatctcc aactaccgtga actggatcca gcagaagccc 120
ggcaaggccc ccaagccctt gatctactac acctccaaacc tgcagtccgg cgtgcctcc 180
cggttctccg gtcggcgtc cgccaccgc tacaccctgtg ccatctccct cctgcagcccc 240
gaggacttcg ccacctacta ctgcattggc gagaccatct ctcctacatc cttcgccag 300
ggcacaagg tggatcaa g 321

SEQ ID NO: 33      moltype = DNA length = 45
FEATURE
source          1..45
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 33
ggtggcggtg gtcggggcg tgggtgggtcg ggtggcgccg gatct 45

SEQ ID NO: 34      moltype = DNA length = 363
FEATURE
source          1..363
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 34
gagggtgcaggc tgggtggagtc cggcgccggc ctgggtgcaggc cggcgccgtc cctgcccgtg 60
tcctgcggccg cttccggctt caccttctcc aacttcgaca tggcctgggt gggcaggcc 120
cccgccagg ggctgggtgt ggtgtccctc atcaccacccg gggccgacca ggccatctac 180
ggccactccg tgaaggggccg gttccaccatc tcccgccgacca acgccaagaa caccctgtac 240
ctgcagatgtg actccctgcg gggcaggac accggcggtg actactgcgt gggcaccggc 300
tactacgacg gttaccaccc tggggccagg gcaccctgtt gaccgtgtcc 360
tcc 363

SEQ ID NO: 35      moltype = DNA length = 165
FEATURE
source          1..165
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 35
ttcgtgcggcc tcttcctgcc agcgaagccc accacgacgc cagcgccggc accaccaaca 60
ccggcgccca ccatacggtc gcaagccctg tccctgcgcc cagaggcggtg cggccagcg 120
ggggggggcg cagtcacac gagggggctg gacttcgcct gtgtat 165

SEQ ID NO: 36      moltype = DNA length = 72
FEATURE
source          1..72
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 36
atttacatct gggccctt ggccggact tgtgggtcc ttctcctgtc actggttatc 60
accctttact gc 72

SEQ ID NO: 37      moltype = DNA length = 126
FEATURE
source          1..126
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 37
aaacggggca gaaagaaaact cctgttatata ttcaaaacac catttatgag accagtacaa 60
actactcaag aggaagatgg ctgttagctgc cgatttccag aagaagaaga aggaggatgt 120
gaactg 126

SEQ ID NO: 38      moltype = DNA length = 339
FEATURE
source          1..339
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 38
agagtgaagt tcagcaggag cgcagacgccc cccgcgtacc agcaggccca gaaccagctc 60
tataaacgacg tcaatctagg acgaagagag gatgtacgtatg ttttggacaa gagacgtggc 120
cggtggaccctg agatgggggg aaagccgaga aggaagaacc ctcaggaaagg cctgtacaat 180
gaactgcaga aagataaat ggcggaggcc tacagtgcata ttggatgaa aggccgacgc 240
cggtggggca agggccacga tggccattac caggtctca gtacagocac caaggacacc 300
tacgacgccc ttcacatgca ggccctgccc cctcgctaa 339

SEQ ID NO: 39      moltype = DNA length = 2250
FEATURE

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SEQUENCE: 42          organism = synthetic construct
gaagtgcagc tgggtggagtc tgggggaggo ttggtagcage ctggcaggct cctgagactc 60
tccctgtcgat cctctggatt caccttaat gattatgcga tgcactgggt cggcaagct 120
ccagggaaagg gcctggagtg ggtctcaact attagttggaa atagttgttc cataggctat 180
ggggactctg tgaagggccg attaccatc tccagagaca acgccaagaa gtccctgtat 240
ctgcaaataatgca acatgtctgag agctgaggac acggccttgtt attactgtgc aaaagatata 300
cagtagccacta ctactacta cggtatggac gtctggggcc aagggaccac ggtcacccgtc 360
tcctca                                         366

SEQ ID NO: 43          moltype = DNA length = 54
FEATURE
source
1..54
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 43
ggcagttacta gcggtgggtgg ctccgggggc ggttccgggtt gggggccgac cagc 54

SEQ ID NO: 44          moltype = DNA length = 321
FEATURE
source
1..321
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 44
gaaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccaggggaa aagagccacc 60
cttcctgcga gggccagtc gagttttagt agtactatgtt cttggatcca acagaaacct 120
ggccaggctc ccaggatctt catctatgtt gcatccaaaca gggccatggg catcccgcc 180
aggttcagtg tcggatgggtc ttcaacttc tccatcagcag ccttagagcc 240
aaagatttt cagtttata ctgtcagcag cgttagcaact ggccgtatcac ctccggccaa 300
gggacacgac tggagattaa a                                         321

SEQ ID NO: 45          moltype = DNA length = 15
FEATURE
source
1..15
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 45
ggaggtgttg gatcc                                         15

SEQ ID NO: 46          moltype = DNA length = 363
FEATURE
source
1..363
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 46
gggtgcagc tgggtggagtc cggccggccgc ctggcgcagc cccggccgtc cctgcggctg 60
tccctgcgcg cctccggctt caccttcacc aacttcgacca tggcctgggt gggccaggcc 120
ccggcaagg gcctgggtgtt ggtgccttc atcaccaccc ggcggacaca cgcctatcac 180
ggccactccg tgaaggcccg gttccatc tccgggacca acgccaagaa caccctgtac 240
ctgcagatga actccctgcg ggccgaggac accggcgtgtt actactgtgtt gggccacggc 300
tactacgacg gttaccatc ttggggccagg gcaccctgtt gaccgtgtcc 360
tcc                                         363

SEQ ID NO: 47          moltype = DNA length = 45
FEATURE
source
1..45
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 47
ggtggccgggtg gtcggggccgg tgggtgggtcg ggtggccggcg gatct                                         45

SEQ ID NO: 48          moltype = DNA length = 321
FEATURE
source
1..321
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 48
gacatccaga tgacccagtc cccctcccttc ctgtccgcct ccgtgggcga ccgggtgacc 60
atcacctggcc gggccctccca gggcatcttc aactaccatgtt actgttacca gcagaaggccc 120
ggcaaggcccc ccaagccccctt gatctactac acctccaaacc tgcagtcggg cgtccctcc 180
ccgttctccg gttccggctc cggccaccac tacaccctgtt ccattcttc cctgcaggccc 240
gaggacttcg ccacctacta ctgtcatgggc cagaccatctt ctccttacac ctccggccag 300
ggcaccacaa g tggagatcaa g                                         321

SEQ ID NO: 49          moltype = DNA length = 165
FEATURE

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source          1..165
               mol_type = other DNA
               organism = synthetic construct

SEQUENCE: 49
ttcgtgcggg tcttcctgcc agcgaagccc accacgacgc cagcgccggc accaccaaca 60
cggcgccca ccatacgctc gcagccccctg tccctgcgcc cagaggcggtg ccggccagcg 120
ggggggggcg cagtgcacac gagggggctg gacttcgcct gtgtat 165

SEQ ID NO: 50      moltype = DNA  length = 72
FEATURE          Location/Qualifiers
source           1..72
               mol_type = other DNA
               organism = synthetic construct

SEQUENCE: 50
atctacatct gggcgccctt ggccggact tgtgggtcc ttctcctgtc actggttatc 60
acccttactt gc 72

SEQ ID NO: 51      moltype = DNA  length = 126
FEATURE          Location/Qualifiers
source           1..126
               mol_type = other DNA
               organism = synthetic construct

SEQUENCE: 51
aaacggggca gaaagaaaact cctgttatata ttcaaacaac cattttagag accagtacaa 60
actactcaag aggaagatgg ctgtagctgc cgatttccag aagaagaaga aggaggatgt 120
gaactg 126

SEQ ID NO: 52      moltype = DNA  length = 339
FEATURE          Location/Qualifiers
source           1..339
               mol_type = other DNA
               organism = synthetic construct

SEQUENCE: 52
agagtgaagt tcagcaggag cgcagacgccc cccgcgttacc agcaggggca gaaccagctc 60
tataaacgacg tcaatcttgg acgaagagag gagtaacgtatg ttttgaccaa gagacgtggc 120
cgggaccctg agatgggggg aaagcggaga aggaagaacc ctcaggaaagg cctgtacaat 180
gaactgcaga aagataaagat ggcggaggccc tacagtggaa ttggatgaa aggccggcgc 240
cgagggggca aggggcacga tggccttac cagggtctca gtacagccac caaggacacc 300
tacgacgccc ttcacatgca ggcctgccc cctcgctaa 339

SEQ ID NO: 53      moltype = DNA  length = 2250
FEATURE          Location/Qualifiers
source           1..2250
               mol_type = other DNA
               organism = synthetic construct

SEQUENCE: 53
atggccttac cagtggaccgc cttgtctctg ccgtggccct tgcgtgttcca cgccggcagg 60
ccggaaatgc agctgggtgg gtctggggga ggcttggatc agcctggcag gtccctgaga 120
cttcctctgg cagcccttgg attcacctt aatgattatg ccatgcactg ggtccggca 180
gctccaggaa agggcccttgg gtgggtctca actattatgtt ggaatagtgg ttccataggc 240
tatgcggact ctgttggggc ccgttccatc atctcccaag acaacgccaa gaatggccctg 300
tatctgcaaa tgaacatgtc gagagatgtt gacacggccct tgatattatgt tgcaaaaatg 360
atacagtagc gcaactacta ctacggatg gacgttggggc gccaaggggac cacggtcacc 420
gtctccttcg cgtacttag cgggtggcgc tccggggggc gttcgggtgg gggccggcagc 480
agcgaatttg tggtagacca gtctccatc accctgttt tgcgtccagg ggaaagagcc 540
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aaagataaaga	tggcgaggc	ctacagttag	atgggatga	aaggcgacgc	ccggaggccc	2160
aaggggcacg	atggccctta	ccagggtctc	agtacagcc	ccaaggacac	ctacgacgcc	2220
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FEATURE	Location/Qualifiers					
source	1..749					
	mol_type = protein					
	organism = synthetic construct					
SEQUENCE: 54						
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IQYGNYYGYM	DWVGQGTTTV	VSSGTSGGGG	SEIVLTQSPA	TLSLSPGERA	180	
TLSGRASRVTI	SSYLAWSQQK	PQQAPRLLIY	DASNRATGIP	ARFSGSGSGT	DFTLTISLE	240
PEDFAVYVCQ	QRSNNPITFG	QGTTRLEIKGG	GGSEVQLVES	GGGLVQPGGS	LRLSCAASGF	300
TFSNFDMAWV	RQAPGKGLVW	VSSITTGADH	AIYADSVKGR	FTISRDNAKN	TLYLQMNSLR	360
AEDTAVYVCV	RHGYYDGYHL	FDYWGQGTLV	TVSSGGGGGG	GGGSGGGGSD	IQMTOQSPSSL	420
SASVGDVRVTI	TCRASQGISN	YLNWYQQKPG	KAPKPLIYTT	SNLQSVPSR	FSGSGSGTDY	480
TLLTISLQPE	DFATYYCMQG	TISSYTFGGQ	TKLEIKFVPV	FLPAKPTTTP	APRPPTPAPT	540
IASQPLSLRP	EACRPAAGGA	VHTRGLDFAC	DIYIWAPLAG	TCGVLLLSLV	ITLYCKRGRK	600
KLLYIFKQPF	MRPVQTQEE	DGCSCRFPPEE	EEGGCELRVK	FSRSADAPAY	QQQNOLYNE	660
LNLGRREYED	VLDKRRGRD	EMGGKPRRK	PQEGLYNELOQ	KDKMAEAYSE	IGMKGERRRG	720
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SEQ ID NO: 55	moltype = DNA	length = 63				
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source	1..63					
	mol_type = other DNA					
	organism = synthetic construct					
SEQUENCE: 55						
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ccg						63

SEQ ID NO: 56	moltype = DNA	length = 321				
FEATURE	Location/Qualifiers					
source	1..321					
	mol_type = other DNA					
	organism = synthetic construct					
SEQUENCE: 56						
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ggccaggctc	ccaggctcc	catctatg	gcatccaa	ggccactgg	catcccagcc	180
aggttcagt	caagtggtc	tgggacag	ttcaacttc	ccatcagcag	cctagagcct	240
gaagatttg	cagtttata	ctgtcagcag	cgttagcaact	ggccgtatcac	cttcggccaa	300
gggacacgac	tggagattaa	a				321

SEQ ID NO: 57	moltype = DNA	length = 54				
FEATURE	Location/Qualifiers					
source	1..54					
	mol_type = other DNA					
	organism = synthetic construct					
SEQUENCE: 57						
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SEQ ID NO: 58	moltype = DNA	length = 366				
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source	1..366					
	mol_type = other DNA					
	organism = synthetic construct					
SEQUENCE: 58						
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ggcgactctg	tgaagggccg	attaccatc	tccagagaca	acgccaagaa	gtccctgtat	240
ctgcaaatga	acagtctgag	agctgaggac	acggccttgt	attactgtgc	aaaagatata	300
cagtacggca	actactacta	cggtatggac	gtctggggcc	aagggaccac	ggtcaccgtc	360
tcctca						366

SEQ ID NO: 59	moltype = DNA	length = 15
FEATURE	Location/Qualifiers	
source	1..15	

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mol_type = other DNA
organism = synthetic construct
SEQUENCE: 59
ggaggtggtg gatcc                                15

SEQ ID NO: 60          moltype = DNA  length = 363
FEATURE
source               Location/Qualifiers
1..363
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 60
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cttcagatcg aactccctcg ggcggaggac accggcggtg actactcggt qccggcacggc 300
tactacgacg gtcaccacct gttcactac tggggccagg gtcaccatgtt gaccgtgtcc 360
tcc                                363

SEQ ID NO: 61          moltype = DNA  length = 45
FEATURE
source               Location/Qualifiers
1..45
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 61
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SEQ ID NO: 62          moltype = DNA  length = 321
FEATURE
source               Location/Qualifiers
1..321
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 62
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ggcaaggcccc caaaggccct gatctactac acctccaaacc tgcaagtccgg cgtgccctcc 180
cggttctccg gtcggcgctc cggcaccgac tacaccctga ccattctctc cctgcagggcc 240
gaggacttcg ccacctaacta ctgcattggc cagaccatct ctcctacac cttcgccag 300
ggcacaaggc tggagatcaa g                                321

SEQ ID NO: 63          moltype = DNA  length = 165
FEATURE
source               Location/Qualifiers
1..165
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 63
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ccggcgcggca ccatcgcgcc gcaagccctg tcctgcgcg cagaggcggtt cggccagcg 120
ggggggggcg cagtgcacac gagggggctg gacttcgcct gtgtat                                165

SEQ ID NO: 64          moltype = DNA  length = 72
FEATURE
source               Location/Qualifiers
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mol_type = other DNA
organism = synthetic construct
SEQUENCE: 64
atctacatct gggccccc ttcttcctggc actgggttac 60
accctttact gc                                72

SEQ ID NO: 65          moltype = DNA  length = 126
FEATURE
source               Location/Qualifiers
1..126
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 65
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actactcaag aggaagatgg ctgttagctgc cgatttccag aagaagaaga aggaggatgt 120
gaactg                                126

SEQ ID NO: 66          moltype = DNA  length = 339
FEATURE
source               Location/Qualifiers
1..339
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 66
agagtgaagt tcagcaggag cgcagacgc ccccgctacc agcagggcca gaaccagctc  60

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tataacgagc tcaatctagg acgaagagag gagtacgatg tttggacaa gagacgtggc	120
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gaactgcaga aagataagat ggcggaggcc tacagtgaga ttggatgaa aggccgacgc	240
cgagggggca aggggcacga tgccattac cagggtctca gtacagccac caaggacacc	300
tacgacgccc ttcacatgca ggccctgccc ctcgctaa	339
SEQ ID NO: 67	moltype = DNA length = 2250
FEATURE	Location/Qualifiers
source	1..2250
	mol_type = other DNA
	organism = synthetic construct
SEQUENCE: 67	
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tttccgcgttgc tttccgcgttgc tttccgcgttgc tttccgcgttgc tttccgcgttgc	8940
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SEQ ID NO: 68	moltype = AA length = 749

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SEQUENCE: 69
atggccttac cagtgaccgc cttgtcctg ccgtgtggct tgcgtgtcca cgccgccagg 60
ccg 63

SEQ ID NO: 70      moltype = DNA length = 321
FEATURE          Location/Qualifiers
source           1..321
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 70
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cttcctcgca gggccagtca gagttttagc agtacttag cttgttacca acagaaaacct 120
ggccaggctc ccaggctct catctatgt gcatccaaca gggccactgg catcccagcc 180
aggttcaatgt gcagtgggtt tggcacacac ttcaacttca ccatacagcag ccttagggct 240
gaagattttgc cagtttata ctgtcagcag cgttagcaact ggccgatcac cttcgccaa 300
gggacacgac tggagattaa a 321

SEQ ID NO: 71      moltype = DNA length = 54
FEATURE          Location/Qualifiers
source           1..54
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 71
ggcagacta ggggtgggtgg ctccgggggc ggttccgggtt gggggccggcag cagc 54

SEQ ID NO: 72      moltype = DNA length = 366
FEATURE          Location/Qualifiers
source           1..366
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 72
gaaagtgcagc tgggtggagtc tggggggggc ttgggtacagc ctggcagggtc cctgagactc 60
tcctgtcgac cctctggatt caccttaat gattatgcac tgcactgggt cggcaagct 120
ccaggaaagg ggcctggagtg ggtctcaact attagttggaa atagttggtc cataggctat 180
ggggactctc tgaaggggcccg attcaccatc tccagagacaa acgccaaggaa gtccctgtat 240
ctgcaaatacga acagtctgag agctgaggac acggcccttg attactgtgc aaaagatata 300
cagtaacggca actactacta cttgtatggac gtcggggggc aaggggaccac ggtcaccgtc 360
tcctca 366

SEQ ID NO: 73      moltype = DNA length = 15
FEATURE          Location/Qualifiers
source           1..15
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 73
ggaggtggtg gatcc 15

SEQ ID NO: 74      moltype = DNA length = 363
FEATURE          Location/Qualifiers
source           1..363
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 74
gagggtgcagc tgggtggagtc cggggggggc ctgggtgcagc cccggccgtc cctggggctg 60
tcctgtcgcc cctccggctt caccttctcc aacttgcaca tggcctgggt gggcaggcc 120
ccggcaagg ggcctgggtg ggtctctcc atcaccaccc ggcggcggaca cgcctatctac 180
ggccactctc tgaaggggcccg gttcaccatc tccggggaca acgccaaggaa caccctgtac 240
ctgcagatga actccctgcg ggccgaggac accggccgtgt actactgcgt gggcaccggc 300
tactacgacg gtcaccatc ttggggccagg gcaccctgtt gaccgtgtcc 360
tcc 363

SEQ ID NO: 75      moltype = DNA length = 45
FEATURE          Location/Qualifiers
source           1..45
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 75
ggtggcggtg gtcggggcg tgggtgggtcg ggtggcggtcg gatct 45

SEQ ID NO: 76      moltype = DNA length = 321
FEATURE          Location/Qualifiers
source           1..321
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 76
gacatccaga tgacccagtc cccctctcc ctgtccgcct ccgtggggcga ccgggtgacc 60

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atcacctgcc	gggcctcca	gggcatctcc	aactaccta	actggtacca	gcagaagccc	120
gccaaggccc	ccaagccccct	gatctactac	accccaacc	tgcagtccgg	cgtccctcc	180
cggttctccg	gtccggcgtc	cgccaccgac	tacaccctga	ccatctcc	cctgcagccc	240
gaggacttcg	ccacctacta	ctgcattggc	cagaccatct	cctcctacac	cttcggccag	300
ggcacaagg	tgaggatcaa	g				321
 SEQ ID NO: 77			moltype = DNA	length = 36		
FEATURE			Location/Qualifiers			
source			1..36			
			mol_type = other DNA			
			organism = synthetic construct			
SEQUENCE: 77						
gagagcaagt	acggaccgccc	ctgccccct	tgcct		36	
 SEQ ID NO: 78			moltype = AA	length = 12		
FEATURE			Location/Qualifiers			
source			1..12			
			mol_type = protein			
			organism = synthetic construct			
SEQUENCE: 78						
ESKYGPPCPP CP					12	
 SEQ ID NO: 79			moltype = DNA	length = 84		
FEATURE			Location/Qualifiers			
source			1..84			
			mol_type = other DNA			
			organism = synthetic construct			
SEQUENCE: 79						
atgttctggg	tgctgggtgg	ggteggggc	gtgctggcct	gctacagcct	gctggtcacc	60
gtggccttca	tcatctttt	ggtg				84
 SEQ ID NO: 80			moltype = AA	length = 28		
FEATURE			Location/Qualifiers			
source			1..28			
			mol_type = protein			
			organism = synthetic construct			
SEQUENCE: 80						
MFWVLVVVGG VLACYSLLVT VAFIIFWV					28	
 SEQ ID NO: 81			moltype = DNA	length = 126		
FEATURE			Location/Qualifiers			
source			1..126			
			mol_type = other DNA			
			organism = synthetic construct			
SEQUENCE: 81						
aaacggggca	gaaagaaaact	cctgttatata	ttcaaacaac	catttatgag	accagtacaa	60
actactcaag	aggaagatgg	ctgtagctc	cgatttccag	aagaagaaga	aggaggatgt	120
gaactg						126
 SEQ ID NO: 82			moltype = DNA	length = 336		
FEATURE			Location/Qualifiers			
source			1..336			
			mol_type = other DNA			
			organism = synthetic construct			
SEQUENCE: 82						
cgggtgaagt	tcagcagaag	cgccgacgcc	cctgcctacc	agcaggccca	aatcagctg	60
tacaacgagc	tgaacctggg	cagaaggaa	gagtagcagg	tcctggat	ggggagggc	120
cgggaccctg	agatggcgg	caagcctcg	cggaagaacc	cccaggaa	gctgtataac	180
gaactgaga	aagacaagat	ggccgaggcc	taacgcaga	tcggcatgaa	gggcgaggcg	240
aggcggggca	aggccacac	cgccctgtat	caggccctgt	ccaccggccac	caaggatacc	300
tacgacgccc	tgcacatgca	ggccctgccc	ccaaagg			336
 SEQ ID NO: 83			moltype = DNA	length = 2133		
FEATURE			Location/Qualifiers			
source			1..2133			
			mol_type = other DNA			
			organism = synthetic construct			
SEQUENCE: 83						
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ccggaaattt	ttgttgacaca	gtctccagcc	accctgtctt	tgtctccagg	ggaaagagcc	120
accctctct	gcagggccag	tcaagtgtt	agcagctact	tagcctggta	ccaaacagaaa	180
cctggccagg	ctcccaggct	cctcatctat	gatgcattca	acagggocac	tggcatccca	240
gccagggc	gtggcgttgg	gtctgggaca	gacttcactc	tcaccatcag	cagccatagag	300
cctgaagat	ttgcagttt	ttactgtcag	cagcgtagca	actggccat	cacccctggc	360
caaggacac	gactggagat	taaaggcgt	actagcggtg	gtggctccgg	gggcgggttcc	420
ggtggggccg	gcagcagcga	agtgcagctg	gtggagtcgt	ggggaggcct	ggtacagcct	480

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ggcagggtccc	ttagactctc	ctgtgcagcc	tctggattca	ccttaatga	ttatgccatg	540
caactgggtcc	ggcaagtc	agggaaaggdc	ctggagtgcc	tctcaactat	tagtggaaat	600
agtgggttcca	taggetatgc	ggactctgt	aagggccat	tcacatctc	cagagacaac	660
gccaagaagt	ccctgtatct	gcaaatgaa	agtctgagag	ctgaggacac	ggccttgtat	720
tactgtgc	aaagataata	gtacggcaac	tactactacg	gtatggacgt	ctggggccaa	780
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ggccggccggcc	tggtgtcagecc	cggeggctcc	ctggggctgt	cctgcgeccg	ctccggcttc	900
accttctcca	acttgcacat	ggcttgggt	cgccaggcccc	ccggcaaggd	cctgggtgtt	960
gtgttctcca	tcaccacccg	cgccgaccac	gcatctacg	ccgactccgt	gaaggccgg	1020
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accctgtacca	tctctccct	gcagcccgag	gacttcgcca	cctactactg	catggccag	1500
accatctct	cctacaccc	cgccaggdc	accaagctgg	agatcaagg	gagcaagta	1560
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gctgttacca	gctgttctgtt	cacccgttcc	ttcatcatct	tttgggtt	acggggcaga	1680
aagaaactcc	tgtatata	caaacaacca	tttatgagac	cagtacaaac	tactcaagag	1740
gaagatggct	gtatgtccg	atttcccgaa	gaagaagaa	gaggatgt	actgcgggt	1800
aagttcagca	gaagcgcgg	cgccccctgc	taccagcagg	gocagaaatca	gtgttacaa	1860
gagctgaa	ttggcagaa	ggaaagatgt	gacgttctgg	ataagccgg	aggccgggac	1920
cctgatgtt	ggggcaagcc	tcggcggaa	aaccccccagg	aaggcctgt	taacgaact	1980
cagaaagaca	agatggccg	ggccatcac	gagatcgca	tgaaggccg	gcccggccgg	2040
gcoaaggccc	acgacggcc	gtatcggtt	ctgtccacc	ccaccaagg	tacctacgac	2100
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FEATURE	Location/Qualifiers	
source	1..710	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 84		
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PGQAPRLLI DASNRATGIP ARFSGSGSGT DFTLTISLLE PEDFAVYYCQ QRSNWPITFG	120	
QGTRLEIKGS TSGGGSGGGS GGGGSEVQL VESGGGLVQP GRSLRLSCAA SGFTFDYAM	180	
HWVRQAPGKG LEWVSTISWN SGSIYADSV KGRFTISRDN AKKSILYLOMN SLRAEDTALY	240	
YCAKDIQYGN YYGYMDWQG GTTVTVSSGG GGSEVQLVES GGGLVQPGGS LRLSCAASGF	300	
TFSNFDMAWV RQAPGKGLVW VSSITTGADH AIYADSVKGR FTISRDNAKN TLYLQMNLSLR	360	
AEDTAVYVCV RHGYDGYHL FDYWGQGTTLV TVSSGGGGGG GGGGGGGSD IQMTQSPSSL	420	
SASVGDRTVI TCRASQGISN YLNWYQKPG KAPKPLIYVV SNLQSGVPSR FSGSGSGTDY	480	
TLTISSLQPE DFATYYCMQG TISSYTFQGQ TKLEIKESKY GPPCPCPMF WVLVVVGVL	540	
ACYSLLVITVA IIIFWVKRGR KKLLYIFKOP FMRPVQTTOE EDGCSCRFPF EEEGGCELRV	600	
KFRSRADAPA YQQQNQLYN ELNLRREEY DVLDKRRGRD PEMGGKPRK NPQEGLYNEL	660	
QDKMRAEYS EIGMKGERRR GKGDHGLYQG LSTATKDTYD ALHMQALPPR	710	

SEQ ID NO: 85	moltype = DNA	length = 63		
FEATURE	Location/Qualifiers			
source	1..63			
	mol_type = other DNA			
	organism = synthetic construct			
SEQUENCE: 85				
atggccttac cagtgttcc	ccgctggcc	tgtgttcca	cgccggccagg	60
ccg				63

SEQ ID NO: 86	moltype = DNA	length = 321				
FEATURE	Location/Qualifiers					
source	1..321					
	mol_type = other DNA					
	organism = synthetic construct					
SEQUENCE: 86						
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ctctccctgca	ggggcagtca	gagtgttagc	agctacttca	acagaaaacct	120	
ggccaggcgtc	ccaggcttct	catctatgt	gcatccaaca	gggcaactgg	180	
aggttcagtg	cgagtgggtc	tgggacagac	tcaactctca	ccatcagcag	ccttagagcct	240
gaagattttg	cagtattata	ctgtcagcag	cgtagcaact	ggccgatcac	cttcggccaa	300
gggacacgac	tggagattaa	a			321	

SEQ ID NO: 87	moltype = DNA	length = 54
FEATURE	Location/Qualifiers	
source	1..54	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 87		

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ggcagacta gcggtggtgg ctccggggc ggttccggtg ggggcggcag cagc	54
SEQ ID NO: 88	moltype = DNA length = 366
FEATURE	Location/Qualifiers
source	1..366
	mol_type = other DNA
	organism = synthetic construct
SEQUENCE: 88	
gaagtgcagc tggggaggc ttggtagccttgcggcactgac 60 tcctgtgcag cctctggatt caccttaat gattatgccttgcggcaagct 120 ccaggaaagg gcctggatgt ggtctcaact attatgttgcataatgttgc 180 ggggactctg tgaaggcccg attaccatc tccagagaca acgccaagaa gtccctgtat 240 ctgcaaataatgc acatgttgc agctggggac acggccttgtt attactgttgc aaaagatata 300 cgttacggca actactacta cggtatggac gtctggggc aagggaccac ggttaccgtc 360 tcctca	366
SEQ ID NO: 89	moltype = DNA length = 15
FEATURE	Location/Qualifiers
source	1..15
	mol_type = other DNA
	organism = synthetic construct
SEQUENCE: 89	
ggaggtggtg gatcc	15
SEQ ID NO: 90	moltype = DNA length = 321
FEATURE	Location/Qualifiers
source	1..321
	mol_type = other DNA
	organism = synthetic construct
SEQUENCE: 90	
gacatccaga tgaccaggc cccctcttc ctgtccgcctt ccgtggggcga ccgggtgacc 60 atcacctgcc gggccctccca gggcatctcc aactacctgttacttgcataccatcgc 120 ggcaaggccc ccaaggccccctt gatctactac accttcaacc ttgcgtccgg cgtccctcc 180 cggttctccg gtcggcgctc cggccacccgttccatccctgttccatccctcc 240 gaggacttcg ccacctacta ctgtatggc gagaccatcttccatccacatccatcc 300 ggcaccaagg tggatcaa g	321
SEQ ID NO: 91	moltype = DNA length = 45
FEATURE	Location/Qualifiers
source	1..45
	mol_type = other DNA
	organism = synthetic construct
SEQUENCE: 91	
ggtggcggtg gtcggcggtt tggtgggtcg ggtggcgccg gatct	45
SEQ ID NO: 92	moltype = DNA length = 363
FEATURE	Location/Qualifiers
source	1..363
	mol_type = other DNA
	organism = synthetic construct
SEQUENCE: 92	
gagggtgcagc tgggtggatgtt cggccggcgc ctgggtcagc cggccggcttc cctggggctg 60 tcctgtgcggc cctccggctt caccttcttc aacttcgaca tggcctgggtt gcccggggcc 120 ccggcaagg gcctgggtgtt ggtgtcttc atcaccaccc gcccggacca cccatctac 180 ggcgactccg tgaaggcccg gttcaccatc tccgggacca acgccaagaa caccctgtac 240 ctgcagatgtt actccctgttgc ggcggaggac accggcgtgtt actactgttgc gggcaccggc 300 tactacgacg gtcaccatcttgcactac tggggccaggc gacccctgtt gaccgttcc 360 tcc	363
SEQ ID NO: 93	moltype = DNA length = 36
FEATURE	Location/Qualifiers
source	1..36
	mol_type = other DNA
	organism = synthetic construct
SEQUENCE: 93	
gagagcaagt acggaccggcc ctggccctt tgccct	36
SEQ ID NO: 94	moltype = DNA length = 84
FEATURE	Location/Qualifiers
source	1..84
	mol_type = other DNA
	organism = synthetic construct
SEQUENCE: 94	
atgttctggg tgctgggtggt ggctggaggc gtgtggccct gctacagctt gctgggttacc 60 gtggcccttca tcattttttggtg	84

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SEQ ID NO: 95	moltype = DNA length = 126
FEATURE	Location/Qualifiers
source	1..126
	mol_type = other DNA
	organism = synthetic construct
SEQUENCE: 95	
aaacggggca gaaagaaaact cctgttatata ttcaaacaac catttatgag accagtacaa	60
actactcaag aggaagatgg ctgtagctgc cgatttccag aagaagaaga aggaggatgt	120
gaactg	126
SEQ ID NO: 96	moltype = DNA length = 336
FEATURE	Location/Qualifiers
source	1..336
	mol_type = other DNA
	organism = synthetic construct
SEQUENCE: 96	
cgggtgaagt tcagcagaag cggcgcacgc cctgcctacc agcaggccca gaatcagctg	60
tacaacgagc tgaacctggg cagaaggaa gagtacgacg tcctggataa gcggagggc	120
cgggaccctg agatggcgcc caagcctg cggagaaggccc cccaggaaagg cctgtataaac	180
gaactgcaga aagacaagat ggccgaggcc tacagcaga tcggcatgaa gggcgagccg	240
aggcggggca agggccacga cggcctgtat cagggcctgt ccaccgcac caaggatacc	300
tacgacgccc tgcacatgca ggcctgccc ccaagg	336
SEQ ID NO: 97	moltype = DNA length = 2133
FEATURE	Location/Qualifiers
source	1..2133
	mol_type = other DNA
	organism = synthetic construct
SEQUENCE: 97	
atggccttac cagtgaccgc cttgtccctg ccgtctggct tgctgtccca cgccgccagg	60
ccggaaattt tggtgacaca gtctcagccg accttgtctt tgcttcagg ggaaagagcc	120
acccctctct gcaggcccg tcagatgtt agcagactact tagcctggta ccaacagaaa	180
cctggccagg ctccccaggct cctcatctat gatgcaccca acagggcac tggcatccca	240
gccagggtca gtggcgttgg gtctgggaca gacttcactc tcaccatcag cagcttagag	300
cctcgaaggatt ttgcgttta ttactgtcag cagcgttagca actggccgtt cacccttcggc	360
caagggacat gactggatata aaaaaggcgt actacgcggtg tggtctccgg gggcggttcc	420
gttggggccg gcaagcgtg agtgcagctg gtggagttt gggggaggcgtt ggtcagccgt	480
ggcagggtccc tgagactctc ctgtgcagcc tctggattca ctttaatga ttatgcatg	540
cactgggtcc ggcacqatcc agggaaaggccg ctggagttgg tctcaactat tagttggaaat	600
agtgggttca atggatgttgc ggactctgtt aaggggccgt tcaccatctc cagagaca	660
gccaagaagt ccctgtatct gcaatgaaat agtctgaaat ctgaggacac ggccttgcata	720
tactgtcata aagatataca gtacggcaac tactactacg gtatggacgt ctggggccaa	780
gggaccacccg tcacccgtctc ctcaaggatgtt ggtggatccg acatccaggat gaccggatcc	840
ccctcttccc tgccgcctcc cgtggcgccg cgggtgacca tcacctgcgg ggcctcccg	900
ggcatacttca ataccatgaa ctggtaccag cagaaggcccc gcaaggcccc caagccctcg	960
atctactaca cctccaaccc tcggatccgcgtt gttccctccc ggttctccgg ctccggatcc	1020
ggcaccggact acaccctgtac ctcggatccgcgtt gttccctccc ggttctccgg ctccggatcc	1080
tgcacccgttccg agaccatcc tccttaacaccc ttccggccagg gcaacaaatgtt ggttccgg	1140
gggtggccgtt gtcggggccg tgggtggccg gatctggatgtt gcaatgttccgg	1200
gagtcggccg cggccctgggtt gcaatgttccgg gatctggatgtt gcaatgttccgg	1260
gggttccactt ttccttccatcc tcggatccgcgtt gttccctccc ggttctccgg ctccggatcc	1320
gtgtgggtgtt ctccttccatcc tcggatccgcgtt gttccctccc ggttctccgg ctccggatcc	1380
ggccgggttca ctatccctccg gcaacaccc ttccggccagg gcaatgttccgg	1440
ctggccggccg aggacacccgc tcggatccgcgtt gttccctccc ggttctccgg ctccggatcc	1500
cacctgttccg actactggggcc tcggatccgcgtt gttccctccc ggttctccgg ctccggatcc	1560
ggaccggccctt gccccccctt tcggatccgcgtt gttccctccc ggttctccgg ctccggatcc	1620
gcctgttaca gctgttccgtt ctcggatccgcgtt gttccctccc ggttctccgg ctccggatcc	1680
aagaaactcc tttatgtatatt caaacaacca ttatgtatatt cttatgtatatt cttatgtatatt	1740
gaagatggct tttatgtatatt caaacaacca ttatgtatatt cttatgtatatt cttatgtatatt	1800
aaatgttccgtt gttccctccc ggttctccgg ctccggatcc gttccctccc ggttctccgg ctccggatcc	1860
gagcttccgtt gttccctccc ggttctccgg ctccggatcc gttccctccc ggttctccgg ctccggatcc	1920
cctggatccgcgtt gttccctccc ggttctccgg ctccggatcc gttccctccc ggttctccgg ctccggatcc	1980
cagaaagaca agatggccga ggcctacago gagatccggca tgaaggccga gccggaggccg	2040
ggcaaggccg acggacggccct gtatccggcc tcggatccgcgtt gttccctccc ggttctccgg ctccggatcc	2100
ggccctgcaca tgcaggccctt gcccccaagg taa	2133
SEQ ID NO: 98	moltype = AA length = 710
FEATURE	Location/Qualifiers
source	1..710
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 98	
MALPVTALL PLALLLHAAR PEIVLTQSPA TLSLSPGERA TLSCRASQSV SSYLAWSQQK	60
PQOAPRLLIY DASN RATGIP ARFSGSGSGT DFTLTISSE PEDFAVYYCQ QRSINWPI TFG	120
QGTTRLEIKGS TSGGGSGGGS GGGGSSEVQL VESGGGLVQP GRSLRLSCAA SGFTFNDYAM	180
HWVRQAPKGK LEWVSTISWN SGSIGYADSV KGRFTISRDNN AKKSLSLYQMN SLRAEDTALY	240

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YCAKDIQYGN YYYGMDVWGQ GTTVTVSSGG GGSDIQMTQS PSSLASAVGD RVTITCRASQ 300
 GISNYLNWYQ QKPGKAPKPL IYYTSNLQSG VPSRFSGSGS GTDYTLTISS LQPEDFATYY 360
 CMGQTISYYT FGQGTTKLEIK GGGGSGGGGS GGGGSEVQLV ESGGGLVQPG GSLRLSCAAS 420
 GFTFSNFDMA WVRQAPGKGL VWFSSITTA DHAIIYADSVK GRFTISRDNA KNTLYLQMNS 480
 LRAEDETAVYY CVRHGYYDGY HLFDYWGQGT LVTVSSESKEY GPPCPCCPMF WVLVVVGVL 540
 ACYSLLVTVA PIIFWVKRGR KKLLYIFKOP FMRPVQTQEE EDGCSCRFPF EEEGGCELRV 600
 KFRSRSDADPA YQQGQNQLYN ELNLGRGRD PEMGGKPRRK NPQEGLYNEL 660
 QDKMKAEEYS EIGMKGERRR GKGDHGLYQG LSTATKDTYD ALHMQALPPR 710

SEQ ID NO: 99 moltype = DNA length = 63
 FEATURE Location/Qualifiers
 source 1..63
 mol_type = other DNA
 organism = synthetic construct
 SEQUENCE: 99 atgcgcattac cagtgaccgc cttgtccctg ccgtggccct tgctgtccca cgccgccagg 60
 ccg 63

SEQ ID NO: 100 moltype = DNA length = 366
 FEATURE Location/Qualifiers
 source 1..366
 mol_type = other DNA
 organism = synthetic construct
 SEQUENCE: 100 gaagtgcagc tgggtggagtc tgggggaggo ttggtacagc ctggcaggc cctgagactc 60
 tcctgtcagc ctctcgatt caccttaat gattatgccca tgcactgggt cccgcagaact 120
 ccaggaaagg gcctggagt ggtctcaact attagttggaa atagttggtc cataggctat 180
 gcccactctg tgaaggcccg attaccatc tccagagaca acgccaagaa gtccctgtat 240
 ctgcataatga acagtcgttag agctgaggac acggccttgtt attactgtgc aaaagatata 300
 cagtagccca actactacta cggtatggac gtctgggccc aagggaccac ggtcacccgc 360
 tcctca 366

SEQ ID NO: 101 moltype = DNA length = 54
 FEATURE Location/Qualifiers
 source 1..54
 mol_type = other DNA
 organism = synthetic construct
 SEQUENCE: 101 ggccgtacta ggggtgggtgg ctccgggggc ggttccgggtg gggggggcag cagc 54

SEQ ID NO: 102 moltype = DNA length = 321
 FEATURE Location/Qualifiers
 source 1..321
 mol_type = other DNA
 organism = synthetic construct
 SEQUENCE: 102 gaattttgtgt tgacacagtc tccagccacc ctgtctttgt ctccaggggaa aagagccacc 60
 ctctctgcga gggccagtc gagttttagc agtacttagt cttgttacca acagaaacct 120
 gggcaggcgc ccaggctctt catctatgtt gcatccaaacca gggccactgg catcccgcc 180
 aggttcagtgc agtggggtc tgggacagac ttcaactctca ccatcagcag cctagagcct 240
 gaagatttt cagtttata ctgtcagcag cgtagcaact gggcgatcac ctccggccaa 300
 gggacacgac tggagatcaa a 321

SEQ ID NO: 103 moltype = DNA length = 15
 FEATURE Location/Qualifiers
 source 1..15
 mol_type = other DNA
 organism = synthetic construct
 SEQUENCE: 103 ggaggtggtg gatcc 15

SEQ ID NO: 104 moltype = DNA length = 321
 FEATURE Location/Qualifiers
 source 1..321
 mol_type = other DNA
 organism = synthetic construct
 SEQUENCE: 104 gacatccaga tgacccagtc cccctcctcc ctgtccgcct ccgtgggcga ccgggtgacc 60
 atcacctgccc gggccctccca gggcatctcc aactacctga actggatccca gcagaagccc 120
 ggcaaggccc ccaagccccct gatctactac acctccaaacc tgcagtcgg cgtgcctcc 180
 cggttctccg gtcctggctc cggcaccgac tacacccctga ccacatctc cctgcagcccc 240
 gaggacttcg ccacctacta ctgcattggc cagaccatct cctcctacac ctccggccag 300
 ggcaccaagg tggagatcaa g 321

SEQ ID NO: 105 moltype = DNA length = 45
 FEATURE Location/Qualifiers

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source          1..45
               mol_type = other DNA
               organism = synthetic construct
SEQUENCE: 105
ggtggcggtg gtcggggcg  tgggtggtcg ggtggccgg  gatct      45
SEQ ID NO: 106      moltype = DNA  length = 363
FEATURE
source          1..363
               mol_type = other DNA
               organism = synthetic construct
SEQUENCE: 106
gagggtgcagc tgggtggagtc cggggggcgc ctgggtgcagc cccggccggtc cctgcggctg  60
tcctgcgcgcg cctccggctt caccccttcc aacttcgacca tggcctgggt gccggcaggcc 120
ccccggcaagg ccctgggtgt ggtgtcttcc atcaccacccg gcccggacca cgccatctac 180
gcccggactcgc tgaaggggcg gttaccatc tccgggacaa acggccaaaggaa caccctgtac 240
ctgcagatgtg actccctgcg ggccgaggac accggcgtgt actactgcgt gcggcacggc 300
tactacgacg gttaccaccc ttggggccagg gcaccctgtgt gaccgtgtcc 360
tcc          363
SEQ ID NO: 107      moltype = DNA  length = 36
FEATURE
source          1..36
               mol_type = other DNA
               organism = synthetic construct
SEQUENCE: 107
gagagcaagt acggaccggcc ctgeccccct tgcacct      36
SEQ ID NO: 108      moltype = DNA  length = 84
FEATURE
source          1..84
               mol_type = other DNA
               organism = synthetic construct
SEQUENCE: 108
atgttctggg tgctgggtgt ggteggaggg gtgtggcct gtcacagcct gctggtcacc 60
gtggccttca tcatttttt ggtg          84
SEQ ID NO: 109      moltype = DNA  length = 126
FEATURE
source          1..126
               mol_type = other DNA
               organism = synthetic construct
SEQUENCE: 109
aaacggggca gaaagaaaact cctgttatata ttcaaacaac catttatgg accagtacaa 60
actactcaag aggaagatgg ctgttagctgc cgatttccag aagaagaaga aggaggatgt 120
gaactg      126
SEQ ID NO: 110      moltype = DNA  length = 336
FEATURE
source          1..336
               mol_type = other DNA
               organism = synthetic construct
SEQUENCE: 110
cgggtgaagt tcagcagaag cggcgaacgc cctgccttacc agcaggccca gaatcagctg 60
tacaacgcgc tgaacctggg cagaaggaa gactacgacg tcctggataa gccggagggc 120
cgggaccctg agatggggcg ccaactcg cggaaagaagg cccaggaaagg cctgtataaac 180
gaactgcaga aagacaagat ggcggaggcc tacacgaga tcggcatgaa gggcgagccg 240
aggcggggca agggccacga cggccctgtat cagggcctgt ccaccgcac caaggatacc 300
tacgacgccc tgcacatgca ggccctggcc ccaagg          336
SEQ ID NO: 111      moltype = DNA  length = 2133
FEATURE
source          1..2133
               mol_type = other DNA
               organism = synthetic construct
SEQUENCE: 111
atggccttac cagtgaccgc cttgtccctg ccgtggccct tgctgtcca cgccggcagg 60
ccggaagtgc agctgggtga gtctggggga ggctgggtac agcctggcag gtccctgaga 120
cttcctgtg cagccctgtgg attcacctt aatgattatg ccatgcactg ggtccggcaa 180
gctccaggaa agggcctggg gtgggtctca actattatgtt ggaatagtgg ttccataggc 240
tatgcggact ctgtgaagggg ccgattcacc atcccaqag acaacgccaa gaagtcctg 300
tatctgcaaa tgaacagtct gagagctgg gacacggccct tggattactg tgcaaaagat 360
atacagtacg gcaactacta ctacggatg gacgtctggg gccaaggac cacggtcacc 420
gtctccctcag gcagtactag cgggtggcggc tccggggggcg gttccgggtt gggcgccagc 480
agcgaatttg tggtgacaca gtctccagec accctgtctt tgctccagg ggaaagagcc 540
accctcttcc gcaaggccag tcagagtgatc agcagactact tagcctggta ccaacagaaa 600

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cctggccagg ctcccaggct cctcatctat gatgcaccca acagggccac tggcatccca 660
gccagggttca gtggcagtgg gtctgggaca gacttcactc tcaccatcg cagccatagag 720
cctgaagatt ttgcgttta ttactgtcag cagcgtagca actggccgt cacccctggc 780
caaggcacac gactggagat taaaggagggt gttggatccg acatccagat gaccaggctcc 840
ccctctccc tgtccgcctc cgtggccgcg cgggtgacca tcacctgcg ggcctcccg 900
ggatctcca actacgtaa ctggtaccag cagaagcccg gcaaggccc caagccctcg 960
atctactaca cctccaaacctt cgatcccggt gtccctccgg gttccctgg ctccggctcc 1020
ggcaccgact acacccctgac catctccctc ctgcagcccg aggacttcgc caccctactac 1080
tgcatggccc agaccatctc ctccatcacacc ttccggcagg gcaccaaggt ggagatcaag 1140
gttggccgggt gtcggccggg ttgggggtcg gttggccggc gatctgggtt gcaatgtgt 1200
gatccgggtt gtcggccggg gcaatccgtt ggttccctgg ggctgttctg cggccctcc 1260
gggttacactt ttcacactt ccacatggcc tgggtggccg aggccccccc caagggctcg 1320
gtgtgggtgt cttccatcac caccggccg gaccacgcg tctacgcga ctccgtgaag 1380
ggccgggttca ccatactccgg ggacaaacccg aagaacacccg tttatcgatca gatgaactcc 1440
ctgcggccggc aggacacccgc cgtgtactac tgcgtccggc acggactacta cgacggctac 1500
caccctgttccg actactgggg ccaggccacc ctggtgaccc tttccctccg qagaagat 1560
ggaccgcctt gccccccctt ccctatgttc tgggtgtcg tgggtgtcg aggccgtgt 1620
gcgtgttaca gctgtgtgtt caccgtggcc ttcatatctt tttgggtgaa acggggcaga 1680
aagaaactcc ttatataatcaaacaacca aaaaacccatc cttatcgatca tactcaagag 1740
gaagatggct gtagctggcg atttcccgaa gaagaagaa gaggatgtga actgcgggt 1800
aagttcagca gaagccgcga cggccctgc acccggcggg taccagcagg gccagaatca gctgtacaac 1860
gagctgaacc tggggcagaag ggaagagtac gacgttccgtt ataagccggag aggccggac 1920
cctgagatgg cggccagaacc tcggccggaa aaccccccggg aaggccctgtt taacgaactg 1980
cagaaagaca agatggccga ggcctacago gatcgccgca tgaaggccga gccggccgg 2040
ggcaaggccc acgacggccctt gtatcgatcc ctgtccaccg ccaccaagga tacctacgac 2100
ggccctgcaca tgcaggccctt gcccccaagg taa 2133

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SEQ ID NO: 112      moltype = AA    length = 710
FEATURE
source          Location/Qualifiers
1..710
mol_type = protein
organism = synthetic construct
SEQUENCE: 112
MALPVTALLL PLALLHAAR PEVQLVESGG GLVQPGRSILR LSCAASGFTF NDYAMHWVRQ 60
APGKGLEWVS TISWNNSGSIG YADSVKGRFT ISRDNAKKSL YLQMNSLRAE DTALYYCAKD 120
IQYGNYYGYM DVWGQGTTVT VSSGSTSGGG SGGGSGGGGG SEIVLTSQSPA TLSLSPGERA 180
TLSCRASQS V SYSLAWYQQK PGQAPRLLIY DASNRATGIP ARFSGSGSGT DFTLTISSE 240
PEDFAVYYCQ QRSNNPITFG QGTTRLEIKGG GGSIDIQMTQS PSSLASAVGD RVTITCRASQ 300
GISNYNLYWQ QKPGKAPKPL IYYTSNLQSQ VPSRFSGSGS GTDYTLTISS LPEDFATYY 360
CMGQTISYYT FGQGTTKLEIK GGGGSGGGGG GGGGSEVQLV ESGGGGLVQPG GSLRLSCAAS 420
GFFFSNPDMA WVRQAPGKGL VVWSSITTGA DHAIYADSVK GRFTISRDNA KNTLYLQMN 480
LRAEDTAVYY CVRHGYYDGY HLFDYWGQGT LVTVSSESKEY GPPCPCPMF WVLVVVVGVL 540
ACYSLLTVVA FIIFWVKRGR KKLYIFKQP FMRPVQTTOE EDGCSCRFPE EEEGGCELRV 600
KFRSRSDADAYA YQQQNQLYN ELNLRQRGRD PEMGGKPRRK NPQEGLYNEL 660
QDKMKAEEERRR EIGMKGERRR GKGDHGLYQG LSTATKDTYD ALHMQALPPR 710

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SEQ ID NO: 113      moltype = DNA   length = 63
FEATURE
source          Location/Qualifiers
1..63
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 113
atggcccttac cagtgaccgc ctgtccctg ccgtggccct tgctgtccca cgccgcagg 60
ccg 63

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SEQ ID NO: 114      moltype = DNA   length = 366
FEATURE
source          Location/Qualifiers
1..366
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 114
gaagtgcagc tgggtggagtc tgggggaggg tgggtacaggc ctggcaggcc cctgagactc 60
tcctgtcgag cctctggatt caccttaat gattatgcga tgcactgggt ccggcaagct 120
ccaggaaagg gcctggatgtt ggttcaactt attagtggaa atagtgttc cataggctat 180
gcggactctg tcaaggccgcg attccatcc tccagagaca acggccaa gtcctgttat 240
ctgcaaatatga acagtcttag agctgaggac acggccctgtt attactgttc aaaagatata 300
cagtagccca actactacta cggtatggac gtctggggcc aaggaccac ggtcaccgtc 360
tcctca 366

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SEQ ID NO: 115      moltype = DNA   length = 54
FEATURE
source          Location/Qualifiers
1..54
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 115
ggcagttacta ggggtgggtgg ctccggggcc ggttccgggtg gggggccggcag cagc 54

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SEQ ID NO: 116      moltype = DNA  length = 321
FEATURE          Location/Qualifiers
source           1..321
                 mol_type = other DNA
                 organism = synthetic construct
SEQUENCE: 116
gaatttgtt tgacacagtc tccagccacc ctgtctttgt ctccaggggta aagagccacc 60
ctctcctgca gggccagtca gagtgtagc agctacttag cctggtagca acagaaacct 120
ggccaggctc ccaggctc catctatgt gcatccaaaca gggccactgg catcccagcc 180
aggttcagtgc caagtgggtc tgggacagac ttactctca ccatcagcag cctagagct 240
gaagatttt cagtttata ctgtcagcag cgtagcaact ggccgtatcac cttcggccaa 300
gggacacgac tggagattaa a                                         321

SEQ ID NO: 117      moltype = DNA  length = 15
FEATURE          Location/Qualifiers
source           1..15
                 mol_type = other DNA
                 organism = synthetic construct
SEQUENCE: 117
ggaggtggtg gatcc                                         15

SEQ ID NO: 118      moltype = DNA  length = 363
FEATURE          Location/Qualifiers
source           1..363
                 mol_type = other DNA
                 organism = synthetic construct
SEQUENCE: 118
gggtgcagc tggtggagtc cggggggcgc ctggcgacgc cggggggctc cctggggctg 60
tccctgcgcg cttccggctt caccttctcc aacttcgacca tggcctgggt gggcaggcc 120
cccgccaaagg gctgtgggtg atcaccaccc gggccggacca cggccatctac 180
ggccgactccg tgaaggggcc gttaccatc tccgggacaa acggcaagaa caccctgtac 240
ctgcagatga actccctgcg ggccgaggac accggcggtg actactgcgt gggcaggcc 300
tactacgacg gttaccaccc tggggccagg gcaccctggt gaccgtgtcc 360
tcc                                         363

SEQ ID NO: 119      moltype = DNA  length = 45
FEATURE          Location/Qualifiers
source           1..45
                 mol_type = other DNA
                 organism = synthetic construct
SEQUENCE: 119
ggtggcggtg gtcggggccg tgggggtcg ggtggcgccg gatct                                         45

SEQ ID NO: 120      moltype = DNA  length = 321
FEATURE          Location/Qualifiers
source           1..321
                 mol_type = other DNA
                 organism = synthetic construct
SEQUENCE: 120
gacatccaga tgacccagtc cccctccctcc ctgtccgcct ccgtggggcga cggggtgacc 60
atcacctgcc gggccctccca gggcatctcc aactacctga actggtagca gcagaagccc 120
ggcaaggcccc ccaagccccct gatctactac acctccaaaccc tgcagtcgg cgtgcccctcc 180
cggttctccg gtcgggctc cggccggac tacaccctga ccatctccctc cctgcagcccc 240
gaggacttcg ccacctaacta ctgcattggc cagaccatct cctcctacac cttcggccag 300
ggcacaaga g tggagatcaa g                                         321

SEQ ID NO: 121      moltype = DNA  length = 36
FEATURE          Location/Qualifiers
source           1..36
                 mol_type = other DNA
                 organism = synthetic construct
SEQUENCE: 121
gagagcaagt acggaccggcc ctgccccct tgcct                                         36

SEQ ID NO: 122      moltype = DNA  length = 84
FEATURE          Location/Qualifiers
source           1..84
                 mol_type = other DNA
                 organism = synthetic construct
SEQUENCE: 122
atgttctggg tgctgggtggt ggtagggcgt gtgtggccct gttacagcct gttgggtacc 60
gtggccctca tcatctttt ggtg                                         84

SEQ ID NO: 123      moltype = DNA  length = 126
FEATURE          Location/Qualifiers

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source          1..126
               mol_type = other DNA
               organism = synthetic construct
SEQUENCE: 123
aaacggggca gaaagaaaact cctgttatata ttcaaacaac catttatgag accagtacaa 60
actactcaag aggaagatgg ctgtagctgc cgatttccag aagaagaaga aggaggatgt 120
gaactg                               126

SEQ ID NO: 124      moltype = DNA  length = 336
FEATURE
source          1..336
               mol_type = other DNA
               organism = synthetic construct
SEQUENCE: 124
cgggtgaagt tcagcagaag cgccgacgc cctgcctacc agcagggcca gaatcagctg 60
tacaacgagc tgaacctggg cagaaggaa qagtacqacg tcctggataa qcggagaggc 120
cgggaccctg agatgggcgg caagectcg cggaagaacc cccaggaagg cctgtataac 180
gaactgcaga aagacaagat ggccgaggcc tacagcaga tcggcatgaa gggcgagcgg 240
aggcggggca agggccacga cggectgtat cagggcctgt ccaccggcac caaggatacc 300
tacgacgccc tgcacatgca ggcctgccc ccaagg                               336

SEQ ID NO: 125      moltype = DNA  length = 2133
FEATURE
source          1..2133
               mol_type = other DNA
               organism = synthetic construct
SEQUENCE: 125
atggccttac cagtgaccgc cttgtcttg ccgcgtggcc tgctgtccca cgccgccagg 60
ccggaagtgc agctggtga gtctggggga ggcttggta acgcattggcag gtccctgaga 120
cttcctctgtg cagcctctgg attcacctt aatgattattt ccattgcactg ggtccggcaa 180
gtctccggga agggcttggg gtgggtctca actattatgtt ggaatagttt ttccataggc 240
tatgcggact ctgtgaaggg ccgatttaccat atctccagag acaacgccaa gaagtccctg 300
tatctgaaaa tgaacagtct gagagcttagt gacacggct ttttattactg tgcaaaagat 360
atacagtacg gcaactacta ctacggatgtt gacgtctggg gccaaggagc cacggtcacc 420
gttcctccatcg gcaactacta ctacggatgtt gacgtctggg gccaaggagc cacggtcacc 480
agcggaaattt tggtgacaca gtctccggcc accctgttctt ttttctccagg gggaaagagcc 540
accctctctt gcagggccag tcagagtgtt agcagctact tagcctgtt ccaacagaaa 600
cctggccagg ctccccaggct cctcatctat gatgcatttca acagggccac tggcatccca 660
gcccagggttca gtggcagggtt gtctggggca gacttccatcg tcacccatcg cagcttagag 720
cctcggatatt tggtgacaca gtctccggcc accctgttctt ttttctccagg gggaaagagcc 780
caaggggacac gactgggatgtt taaaggaggtt ggtggatccg aggtgcacgtt ggtggatcc 840
ggcgccggcc tggtgcagcc cgccggctgtt ctgcggccgc ctccggcttc 900
acccttccca acttcggatgtt ggtggatccg cggcaggccac ccggcaagggg cctgggtgtgg 960
gtgttccatcg tcaaccatcg ccggcaggccac ccgttccatcg ggtggatccg 1020
tttccatcg tcaaccatcg ccggcaggccac ccgttccatcg ggtggatccg 1080
ggcgaggaca ccggcgtgtt ctactgcgtt ccggcaggccac ccgttccatcg 1140
tttccatcg tcaaccatcg ccggcaggccac ccgttccatcg ggtggatccg 1200
gggtgggggtt ccggcaggccac ccgttccatcg ggtggatccg 1260
ccggcgtgtt ccggcaggccac ccgttccatcg ggtggatccg 1320
tacactgttccatcg tcaaccatcg ccggcaggccac ccgttccatcg ggtggatccg 1380
tcaaccatcg tcaaccatcg ccggcaggccac ccgttccatcg ggtggatccg 1440
accctgttccatcg tcaaccatcg ccggcaggccac ccgttccatcg ggtggatccg 1500
accatcttccatcg tcaaccatcg ccggcaggccac ccgttccatcg ggtggatccg 1560
ggaccggccctt ccgttccatcg tcaaccatcg ccggcaggccac ccgttccatcg ggtggatccg 1620
gcgttccatcg tcaaccatcg ccggcaggccac ccgttccatcg ggtggatccg 1680
aagaaactcc ttttccatcg tcaaccatcg ccggcaggccac ccgttccatcg ggtggatccg 1740
gaagatggctt ccggcgtgtt ccggcaggccac ccgttccatcg ggtggatccg 1800
aagttccatcg tcaaccatcg ccggcaggccac ccgttccatcg ggtggatccg 1860
gacgttccatcg tcaaccatcg ccggcaggccac ccgttccatcg ggtggatccg 1920
cctggatggcc tcaaccatcg ccggcaggccac ccgttccatcg ggtggatccg 1980
cagaaagaca agatggccgc tcaaccatcg ccggcaggccac ccgttccatcg ggtggatccg 2040
ggcaaggccc acgacggccctt ccggcaggccac ccgttccatcg ggtggatccg 2100
ggccctgcaca tcaaccatcg ccggcaggccac ccgttccatcg ggtggatccg 2133

SEQ ID NO: 126      moltype = AA  length = 710
FEATURE
source          1..710
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 126
MALPVTALLL PLALLLHAAR PEVQLVESGG GLVQPGRLSLR LSCAASGFTF NDYAMHWVRQ 60
APGKGLEWVS TISWNNSGSIG YADSVKGRFT ISRDNAKKSL YLQMNSLRAE DTALYYCAKD 120
IQYGVNYYGYM DVWGQGTTVT VSSGSTSGGG SGGGGGGGGG SEIVLTLQSPA TLSLSPGERA 180
TLSCRASQSV SSYLAQYQQK PGQAPRLLIY DASN RATGIP ARFSGSGSGT DFTLTISSL 240
PEDFAVYYCQ QRSNWPIFG QGTRLEIKGG GGSEVQLVES GGGLVQPGGS LRLSCAASGF 300
TFSNFDMAWV RQAPGKGLVW VSSITTGADH AIYADSVKGR FTISRDNAKN TLYLQMNSLR 360

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AEDTAVYYCV RHGYYDGYHL FDYWGQGTIV TVSSGGGGSG GGGSGGGGSD IQMTQSPSSL	420
SASVGDRVTI TCRASQGISN YLNWYQQKPG KAPKPLIYTT SNLQSGVPSR FSGSGSGTDY	480
TLTISSLQPE DFATYYCMQG TISSYTEFGQG TKLEIKESKY GPPCPPCMFM WVLVVVGGVL	540
ACYSLLVTVA PIIFWVKRGK KKLLYIFKQP FMRPVQTTOE EDGCSCRFPF EEEGGCELRV	600
KFSRSADAPA YQQQNQLYN ELNLGRREEY DVLDRRRGRD PEMGGKPRK NPQEGLYNEL	660
QDKMMAEAYS EIGMKGERRR GKGDGLYQG LSTATKDTYD ALHMQALPPR	710
SEQ ID NO: 127 moltype = AA length = 6	
FEATURE Location/Qualifiers	
source 1..6	
mol_type = protein	
organism = synthetic construct	
SEQUENCE: 127	
NDYAMH	6
SEQ ID NO: 128 moltype = AA length = 17	
FEATURE Location/Qualifiers	
source 1..17	
mol_type = protein	
organism = synthetic construct	
SEQUENCE: 128	
TISWNNSGSIG YADSVKG	17
SEQ ID NO: 129 moltype = AA length = 13	
FEATURE Location/Qualifiers	
source 1..13	
mol_type = protein	
organism = synthetic construct	
SEQUENCE: 129	
DIQYGNYYYG MDV	13
SEQ ID NO: 130 moltype = AA length = 11	
FEATURE Location/Qualifiers	
source 1..11	
mol_type = protein	
organism = synthetic construct	
SEQUENCE: 130	
RASQSVSSYL A	11
SEQ ID NO: 131 moltype = AA length = 7	
FEATURE Location/Qualifiers	
source 1..7	
mol_type = protein	
organism = synthetic construct	
SEQUENCE: 131	
DASN RAT	7
SEQ ID NO: 132 moltype = AA length = 9	
FEATURE Location/Qualifiers	
source 1..9	
mol_type = protein	
organism = synthetic construct	
SEQUENCE: 132	
QQRSNWPIT	9
SEQ ID NO: 133 moltype = AA length = 23	
FEATURE Location/Qualifiers	
source 1..23	
mol_type = protein	
organism = synthetic construct	
SEQUENCE: 133	
DIQMTQSPSS LSASVGDRVT ITC	23
SEQ ID NO: 134 moltype = AA length = 11	
FEATURE Location/Qualifiers	
source 1..11	
mol_type = protein	
organism = synthetic construct	
SEQUENCE: 134	
RASQGISNYL N	11
SEQ ID NO: 135 moltype = AA length = 15	
FEATURE Location/Qualifiers	
source 1..15	
mol_type = protein	
organism = synthetic construct	

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SEQUENCE: 135 WYQQKPGKAP KPLIY	15
SEQ ID NO: 136 FEATURE source moltype = AA length = 7 Location/Qualifiers 1..7 mol_type = protein organism = synthetic construct	
SEQUENCE: 136 YTSNLQSQ	7
SEQ ID NO: 137 FEATURE source moltype = AA length = 32 Location/Qualifiers 1..32 mol_type = protein organism = synthetic construct	
SEQUENCE: 137 GVPSRFSGSG SGTDYTLTIS SLQPEDFATY YC	32
SEQ ID NO: 138 FEATURE source moltype = AA length = 9 Location/Qualifiers 1..9 mol_type = protein organism = synthetic construct	
SEQUENCE: 138 MGQTISYYT	9
SEQ ID NO: 139 FEATURE source moltype = AA length = 10 Location/Qualifiers 1..10 mol_type = protein organism = synthetic construct	
SEQUENCE: 139 FGQGTKLEIK	10
SEQ ID NO: 140 FEATURE source moltype = AA length = 30 Location/Qualifiers 1..30 mol_type = protein organism = synthetic construct	
SEQUENCE: 140 EVQLVESGGG LVQPGGSLRL SCAASGFTFS	30
SEQ ID NO: 141 FEATURE source moltype = AA length = 5 Location/Qualifiers 1..5 mol_type = protein organism = synthetic construct	
SEQUENCE: 141 NFDMA	5
SEQ ID NO: 142 FEATURE source moltype = AA length = 14 Location/Qualifiers 1..14 mol_type = protein organism = synthetic construct	
SEQUENCE: 142 WVRQAPGKGL VWVS	14
SEQ ID NO: 143 FEATURE source moltype = AA length = 17 Location/Qualifiers 1..17 mol_type = protein organism = synthetic construct	
SEQUENCE: 143 SITTGADHAI YADSVKG	17
SEQ ID NO: 144 FEATURE source moltype = AA length = 32 Location/Qualifiers 1..32 mol_type = protein organism = synthetic construct	
SEQUENCE: 144 RFTISRDNAK NTLYLQMNSL RAEDTAVYYC VR	32
SEQ ID NO: 145	moltype = AA length = 12

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FEATURE source	Location/Qualifiers 1..12 mol_type = protein organism = synthetic construct	
SEQUENCE: 145 HGYYDGYHLF DY		12
SEQ ID NO: 146 FEATURE source	moltype = AA length = 11 Location/Qualifiers 1..11 mol_type = protein organism = synthetic construct	
SEQUENCE: 146 WGGQGTLVTVS S		11

1. A bispecific chimeric antigen receptor (CAR), comprising:
 - (i) an anti-CD20 antigen-binding region which comprises a light chain variable region (V_L 1) and a heavy chain variable region (V_H 1), wherein V_L 1 comprises three complementarity determining regions (CDRs), CDR1, CDR2 and CDR3, having amino acid sequences set forth in SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, respectively, and wherein V_H 1 comprises three CDRs, CDR1, CDR2 and CDR3, having amino acid sequences set forth in SEQ ID NO: 127, SEQ ID NO: 128, SEQ ID NO: 129, respectively; and
 - (ii) an anti-BCMA antigen-binding region which comprises a light chain variable region (V_L 2) and a heavy chain variable region (V_H 2), wherein V_L 2 comprises three complementarity determining regions (CDRs), CDR1, CDR2 and CDR3, having amino acid sequences set forth in SEQ ID NO: 134, SEQ ID NO: 136, SEQ ID NO: 138, respectively, and wherein V_H 2 comprises three CDRs, CDR1, CDR2 and CDR3, having amino acid sequences set forth in SEQ ID NO: 141, SEQ ID NO: 143, SEQ ID NO: 145, respectively.
2. The bispecific CAR of claim 1, wherein V_L 1 is located at the N-terminus of V_H 1.
3. The bispecific CAR of claim 1, wherein V_L 2 is located at the N-terminus of V_H 2.
4. The bispecific CAR of claim 1, wherein V_H 1 is located at the N-terminus of V_L 1.
5. The bispecific CAR of claim 1, wherein V_H 2 is located at the N-terminus of V_L 2.
6. The bispecific CAR of claim 1, wherein V_L 1 and V_H 1 comprise amino acid sequences set forth in SEQ ID NO: 4 and SEQ ID NO: 8, respectively.
7. The bispecific CAR of claim 1, wherein V_L 2 and V_H 2 comprise amino acid sequences set forth in SEQ ID NO: 12 and SEQ ID NO: 16, respectively.
8. The bispecific CAR of claim 1, wherein the anti-CD20 antigen-binding region is a single-chain variable fragment (scFv) that specifically binds CD20, and wherein the anti-BCMA antigen-binding region is a scFv that specifically binds BCMA.
9. The bispecific CAR of claim 1, wherein the bispecific CAR further comprises one or more of the following:
 - (a) a signal peptide,
 - (b) a hinge region,
 - (c) a transmembrane domain,
 - (d) a co-stimulatory region, and
 - (e) a cytoplasmic signaling domain.
10. The bispecific CAR of claim 9, wherein the co-stimulatory region comprises a co-stimulatory region of 4-1BB (CD137), CD28, OX40, CD2, CD7, CD27, CD30, CD40, CD70, CD134, PD1, Dap10, CDS, ICAM-1, LFA-1 (CD11a/CD18), ICOS (CD278), NKG2D, GITR, TLR2, or combinations thereof.
11. The bispecific CAR of claim 9, wherein the cytoplasmic signaling domain comprises a cytoplasmic signaling domain of CD3 ζ .
12. The bispecific CAR of claim 9, wherein the hinge region comprises a hinge region of IgG4, CD8, CD28, CD137, or combinations thereof.
13. The bispecific CAR of claim 9, wherein the transmembrane domain comprises a transmembrane domain of CD8, CD28, CD3 ϵ , CD45, CD4, CD5, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137, CD154, or combinations thereof.
14. The bispecific CAR of claim 1, comprising an amino acid sequence about 80% to about 100% identical to the amino acid sequence set forth in SEQ ID NO:26, SEQ ID NO:40, SEQ ID NO:54, SEQ ID NO:68, SEQ ID NO:84, SEQ ID NO:98, SEQ ID NO:112, or SEQ ID NO:126.
15. An immune cell expressing the bispecific CAR of claim 1.
16. The immune cell of claim 15, wherein the immune cell is a T cell or a natural killer (NK) cell.
17. A nucleic acid encoding the bispecific CAR of claim 1.
18. A vector comprising the nucleic acid of claim 17.
19. A pharmaceutical composition, comprising the bispecific CAR of claim 1.
20. A pharmaceutical composition, comprising the immune cell of claim 15.

* * * * *