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**BISPECIFIC CHIMERIC ANTIGEN RECEPTORS TARGETING CD20 AND BCMA**

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### **Abstract**

5 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.

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## **BISPECIFIC CHIMERIC ANTIGEN RECEPTORS TARGETING CD20 AND BCMA**

### CROSS REFERENCE TO RELATED APPLICATIONS

5 The present application claims divisional status from Australian Patent Application No. 2024244733 filed on 29 March 2024, which in turn claims priority to U.S. Provisional Patent Application Nos. 63/493,495 (filed on March 31, 2023) and 63/509,371 (filed on June 21, 2023), and each of which is hereby incorporated by reference in its entirety.

### INCORPORATION-BY-REFERENCE OF SEQUENCE LISTING

10 A sequence listing, filed as the XML file "11299\_011840-WO0\_SL.xml" which was created on March 26, 2024 and is 168,342 bytes in size, is incorporated herein by reference in its entirety.

### FIELD OF THE INVENTION

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

### BACKGROUND

20 A reference herein to a patent document or any other matter identified as prior art, is not to be taken as an admission that the document or other matter was known or that the information it contains was part of the common general knowledge as at the priority date of any of the claims.

25 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  
30 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).

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.

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 antinuclear antibodies (ANAs), which can mediate SLE pathogenesis 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<sup>hi</sup>T-bet<sup>+</sup> 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<sup>hi</sup>T-bet<sup>+</sup> 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.

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)).

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

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

## SUMMARY

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

5 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<sub>H2</sub> 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.

10 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<sub>L1</sub>) and a heavy chain variable region (V<sub>H1</sub>); and (ii) an anti-BCMA antigen-binding region which comprises a light chain variable region (V<sub>L2</sub>) and a heavy chain variable region (V<sub>H2</sub>).

In one embodiment, V<sub>L1</sub> is located at the N-terminus of V<sub>H1</sub>. In one embodiment, V<sub>H1</sub> is located at the N-terminus of V<sub>L1</sub>. In one embodiment, V<sub>L2</sub> is located at the N-terminus of V<sub>H2</sub>. In one embodiment, V<sub>H2</sub> is located at the N-terminus of V<sub>L2</sub>.

15 In certain embodiments, V<sub>L1</sub> and V<sub>H1</sub> 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.

20 In certain embodiments, V<sub>L2</sub> and V<sub>H2</sub> 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.

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.

25 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.

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

30 The transmembrane domain may comprise a transmembrane domain of CD8, CD28, CD3ε, CD45, CD4, CD5, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137, CD154, or combinations thereof.

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.

The cytoplasmic signaling domain may comprise a cytoplasmic signaling domain of CD3 $\zeta$ .

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.

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.

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

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

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

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.

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.

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

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.

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.

The immune cell may be allogeneic or autologous.

Unless the context requires otherwise, where the terms "comprise", "comprises", "comprised" or "comprising" are used in this specification (including the claims) they are to

be interpreted as specifying the presence of the stated features, integers, steps or components, but not precluding the presence of one or more other features, integers, steps or components, or group thereof.

## BRIEF DESCRIPTION OF THE DRAWINGS

**Figure 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 $\zeta$ ). A short IgG4 hinge (12 aa) and a CD28 transmembrane 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<sub>H</sub> and V<sub>L</sub> in the two scFv sequences are included in the two groups of CARs (TOB1-4 and TOBL1-4). TOBL1 is also named C-CAR168.

**Figure 2** shows the expression level of anti-CD20 and anti-BCMA CARs on the surface of the T cells.

**Figures 3A-3C** show the levels of IFN- $\gamma$  secreted by the activated CAR-T cells *in vitro* in the cell culture supernatant. Figure 3A shows the levels of IFN- $\gamma$  secreted by the TOB1 to TOB4 CAR-T cells in the cell culture supernatant. Figure 3B shows the levels of IFN- $\gamma$  secreted by the TOBL1 to TOBL4 CAR-T cells in the cell culture supernatant. Figure 3C: TOBL1 to TOBL4 showed high level IFN- $\gamma$  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.

**Figures 4A-4B** show the expression levels of CD137 on the surface of the activated CAR-T cells.

**Figures 5A-5B** show the *in vitro* cytotoxicity of CAR-Ts cells (Figure 5A: TOB1 to TOB4; Figure 5B: TOBL1 to TOBL4) by RTCA assays.

**Figures 6A-6C:** C-CAR168 shows robust potency against CD20+ and BCMA+ cells *in vitro*. Figure 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). Figure 6B shows the release of IFN- $\gamma$  after the CAR-T cells were co-cultured with CD20-positive and/or BCMA-positive target cells. Figure 6C shows the cytotoxicity of the CAR-T cells targeting CD20 and/or BCMA, at different E:T ratios.

**Figures 7A-7C:** Cytotoxicity of C-CAR168 on ABC-enriched B cells *in vitro*. Figure 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. Figure 7B: Differentiation of ABCs. The lower panels show that the proportion of ABC subpopulations increased significantly after induction of differentiation of autologous B cells. Figure 7C: Cytolysis of ABC-enriched B cells by C-CAR168 at different E:T ratios.

**Figures 8A-8D:** C-CAR168 bears no cross-reactivity against human membrane proteome. Figures 8A-8B: C-CAR168 scFv-RabFc binding specificity in the membrane protein array. Figure 8C: Flow cytometry detection of expression of ITGB2-ITGAM and ITGB2-ITGAL in 293T cells. Figure 8D (left panel): Flow cytometric detection of the proportion of 4-1BB-positive cells. Figure 8D (right panel): Flow cytometry detection of IFN- $\gamma$  concentrations in the co-culture supernatants.

**Figures 9A-9G:** *In vivo* cytotoxicity of C-CAR168 in tumor-bearing mice. Figure 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. Figure 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. Figure 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. Figure 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. Figures 9E-9G: C-CAR168 significantly inhibited the growth of K562-CD20-BCMA tumor cells in B-NDG tumor bearing mice. Figure 9E: Tumor growth curve of each group during the experiment. Figure 9F: The survival rate curve of each group during the experimental period. Figure 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.

**Figures 10A-10D:** C-CAR168 shows robust potency *in vitro* against autologous B cells from SLE patients. Figure 10A: T cells from eight SLE patients were successfully transduced by lentiviral vectors encoding C-CAR168 and expressed the anti-CD20/BCMA CAR. Figure 10B: C-CAR168 CAR-T cells generated from the SLE patient samples showed robust activity (IFN- $\gamma$  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. Figure 10C: C-CAR168 CAR-T cells generated from the SLE patient samples showed robust activity

(e.g., IFN- $\gamma$  release) against pan B cells isolated from the SLE patients. Figure 10D: Pan B cells isolated from the SLE patients were recognized and lysed by autologous C-CAR168 cells.

#### DETAILED DESCRIPTION

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.

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.

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  $\text{Ca}^{2+}$  conductance.

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 ( $V_{H2}$ ).

The present bispecific chimeric antigen receptor (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 ( $V_{H1}$ ) 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.

5 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: 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: 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: 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.

20 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  $V_{H2}$ .

25 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.

30 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.

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.

5 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.

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.

10 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.

15 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.

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.

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

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.

25 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.

30 The transmembrane domain may comprise a transmembrane domain of (or may be derived from) CD8, CD28, CD3ε, CD45, CD4, CD5, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137, CD154, or combinations thereof.

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.

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.

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.

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.

The cytoplasmic signaling domain may comprise a cytoplasmic signaling domain of (or may be derived from) CD3 $\zeta$ . 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.

The present CAR may comprise a linker (linker-1) between V<sub>L</sub> and V<sub>H</sub> 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.

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.

The present CAR may comprise a linker (linker-3) between V<sub>L</sub> and V<sub>H</sub> 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.

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<sub>L1</sub>) 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.

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

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.

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.

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  $V_{H2}$ .

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.

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.

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.

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.

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.

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.

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

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.

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.

5 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.

10 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.

15 The pharmaceutical composition may comprise the present immune cells at a concentration ranging from about  $1 \times 10^3$  cells/mL to about  $1 \times 10^8$  cells/mL, or from about  $1 \times 10^4$  cells/mL to about  $1 \times 10^7$  cells/mL.

20 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.

The immune cell may be allogeneic or autologous.

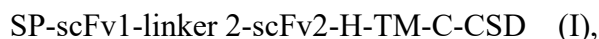
The autoimmune disorder may be systemic lupus erythematosus (SLE) (e.g., lupus nephritis), systemic sclerosis (SSc), inflammatory myopathy (e.g., polymyositis, dermatomyositis, or inclusion-body myositis), systemic scleroderma, multiple sclerosis, or neuromyelitis optica (NMO).

25 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.

30 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).

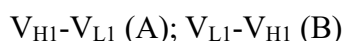
The present disclosure provides a chimeric antigen receptor (CAR), wherein the structure of the chimeric antigen receptor may be shown in formula I:



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.

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.

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



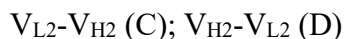
wherein  $V_{H1}$  is an anti-CD20 antibody heavy chain variable region;  $V_{L1}$  is an anti-CD20 antibody light chain variable region; and "-" is a linker peptide or a peptide bond.

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

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.

$V_{L1}$  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.

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.

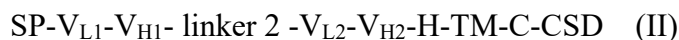
In one embodiment, the present CAR has an anti-BCMA antigen binding domain with a structure as shown in formula C.

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.

$V_{L2}$  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.

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



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

In certain embodiments, the anti-CD20 antigen-binding region includes a light chain variable region ( $V_L$ ) comprising an amino acid sequence 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 the amino acid sequence set forth in SEQ ID NO: 4.

In certain embodiments, the anti-CD20 antigen-binding region includes a heavy chain variable region ( $V_H$ ) comprising an amino acid sequence 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 the amino acid sequence set forth in SEQ ID NO: 8.

In certain embodiments, the anti-BCMA antigen-binding region includes a light chain variable region ( $V_L$ ) comprising an amino acid sequence 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 the amino acid sequence set forth in SEQ ID NO: 12.

In certain embodiments, the anti-BCMA antigen-binding region includes a heavy chain variable region ( $V_H$ ) comprising an amino acid sequence 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 the amino acid sequence set forth in SEQ ID NO:16.

A light chain variable region ( $V_L$ ) of the anti-CD20 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 24-34, position 50-56, position 89-97 of SEQ ID NO:4, respectively (the CDRs of a light chain variable region of the Ofatumumab antibody).

A light chain variable region ( $V_L$ ) of the anti-CD20 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: 130, SEQ ID NO: 131, SEQ ID NO: 132, respectively (the CDRs of a light chain variable region of the Ofatumumab antibody).

A heavy chain variable region ( $V_H$ ) of the anti-CD20 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 30-35, position 50-66, position 99-111 of SEQ ID NO:8, respectively (the CDRs of a heavy chain variable region of the Ofatumumab antibody).

A heavy chain variable region ( $V_H$ ) of the anti-CD20 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: 127, SEQ ID NO: 128, SEQ ID NO: 129, respectively (the CDRs of a heavy chain variable region of the Ofatumumab antibody).

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 position 24-34, position 50-56, position 89-97 of SEQ ID NO: 4, respectively (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 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).

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).

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%,  
5 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  
10 of a light chain variable region of the BCMA-20 antibody).

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  
15 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  
20 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).

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  
25 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  
30 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).

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).

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).

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).

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.

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

EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQKPGQAPRLLIYDASNRATGI PARFSGSGSGTDFLTLSLEPEDFAVYYCQQRSNWPITFGQGTRLEIK (SEQ ID NO: 4)

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

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

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

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

EVQLVESGGGLVQPGRSLRLSCAASGFTFNDYAMHWVRQAPGKGLEWVSTTISWNS  
GSIGYADSVKGRFTISRDNAKKSLYLQMNSLRAEDTALYYCAKDIQYGNYYYYGMD  
YWGQGTTVTVSS (SEQ ID NO: 8)

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

OF-VH-CDR2: SEQ ID NO: 8, position 50-66. The sequence of OF-VH-CDR2 is: TISWNSGSIGYADSVKG (SEQ ID NO: 128).

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

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.

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

DIQMTQSPSSLSASVGRVTITCRASQGISNYLNWYQQKPGKAPKPLIYYTSNLQSGV  
PSRFSGSGSGTDYTLTISSLQPEDFATYYCMGQTISSYTFGQGTKLEIK (SEQ ID  
NO:12)

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

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

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

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

EVQLVESGGGLVQPGGSLRLSCAASGFTFSNFDMAWVRQAPGKGLVWVSSITGAD  
HAIYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCVRHGYYDGYHLFDYW  
GQGTLVTVSS (SEQ ID NO:16)

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

B20-VH-CDR2: SEQ ID NO: 16, position 50-66. The sequence of B20-VH-CDR2 is:  
SITGADHAIYADSVKG (SEQ ID NO: 143).

10 B20-VH-CDR3: SEQ ID NO: 16, position 99-110. The sequence of B20-VH-CDR3 is:  
HGYDGYHLFDY (SEQ ID NO: 145).

The signal peptide may be the signal peptide of CD8, having the following sequence:  
MALPVTALLLPLALLLHAARP (SEQ ID NO:2)

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)

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

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: GGGSGGGSGGGGS (SEQ ID NO:14)

20 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.

The hinge region may be derived from CD8a which has the following sequence:  
FVPVFLPAKPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACD (SEQ  
ID NO:18)

25 The hinge region may be derived from IgG4 which has the following sequence:  
ESKYGPPCPPCP (SEQ ID NO:78)

The transmembrane domain may be derived from CD8 (CD8TM) which has the  
following sequence: IYIWAPLAGTCGVLLLSLVITLYC (SEQ ID NO:20)

30 The transmembrane domain may be derived from CD28 (CD28TM) which has the  
following sequence: MFWVLVVVGGVLACYSLLVTVAFIIFWV (SEQ ID NO:80)

The co-stimulatory region may be derived from 4-1BB which has the following  
sequence:

KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEEGGCEL (SEQ ID NO:22)

The cytoplasmic signaling domain may be derived from CD3 $\zeta$  which has the following

sequence:

RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKN  
PQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM  
QALPPR (SEQ ID NO:24)

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### **Chimeric antigen receptors (CARs)**

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. 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.

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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;

5 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.

10 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  
15 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.

20 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  
25 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.

30 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 $\alpha$  or CD28 $\alpha$ . In some embodiments, the hinge domain is a portion of the hinge domain of CD8 $\alpha$ , 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 $\alpha$  or CD28 $\alpha$ .

Hinge domains of antibodies, such as an IgG, IgA, IgM, IgE, or IgD antibody, are

5 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.

15 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)<sub>n</sub> (or (GxS)<sub>n</sub>) 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.

20 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.

25 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.

30 In some embodiments, the transmembrane domain is that of CD8 $\alpha$ . In some embodiments, the transmembrane domain is that of CD28. In some embodiments, the transmembrane domain is that of ICOS.

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.

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.

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.

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).

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.

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 ( $\zeta$  chain portion)).

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.

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**

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.

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<sup>+</sup>) or CD8 and CD4 (CD8<sup>+</sup>/CD4<sup>+</sup>). In some embodiments, the T cells are T cells of an established T cell line, for example, Jurkat cells.

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.

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.

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.

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.

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.

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.

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.

5 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.

### 10 **Vectors**

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

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

15 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.

20 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- $\alpha$ ) promoter with or without the EF1- $\alpha$  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.

30 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.

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).

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.

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).

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.

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.

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**

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  $1 \times 10^3$ - $1 \times 10^8$  cells/mL, or  $1 \times 10^4$ - $1 \times 10^7$  cells/mL.

5 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 10 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.

15 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.

20 The present pharmaceutical composition may be delivered to a cell by contacting the cell with the present pharmaceutical composition.

25 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, sub-arachinoid, 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.

30 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.

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.

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.

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.

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,  $1 \times 10^6$  to  $1 \times 10^{10}$  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**

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

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 (LLPCs) to reduce/eradicate autoantibody production.

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.

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 antibody-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).

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.

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 arcata, 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,

5 Goodpasture's syndrome, Chagas' disease, sarcoidosis, rheumatic fever, asthma, recurrent abortion, anti-phospholipid syndrome, farmer's lung, erythema multiforme, post cardiectomy 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-Schonlein 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.

20 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, 25 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, 30 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, fibromyositis, lupus, vitiligo, and Guillane-Barre syndrome.

The autoimmune diseases include inflammatory bowel disease (IBD), ulcerative colitis,

5 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, spondyloarthritis, 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-Schoenlejn 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 variable immunodeficiency (common variable hypogammaglobulinaemia), 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 spondy litis 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

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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 vasculitis 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.

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.

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

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.

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

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

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.

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

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.

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.

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 erythroleukemia), 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.

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**

5 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.

10 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  
15 subject who is in need of the treatment.

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.

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

### **Embodiments**

Embodiment 1. 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<sub>H2</sub> 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.

Embodiment 2. A bispecific chimeric antigen receptor (CAR), comprising:

(i) an anti-CD20 antigen-binding region which comprises a light chain variable region (V<sub>L1</sub>) and a heavy chain variable region (V<sub>H1</sub>); and

(ii) an anti-BCMA antigen-binding region which comprises a light chain variable region (V<sub>L2</sub>) and a heavy chain variable region (V<sub>H2</sub>).

Embodiment 3. The bispecific CAR of Embodiment 1 or 2, wherein V<sub>L1</sub> is located at the N-terminus of V<sub>H1</sub>.

Embodiment 4. The bispecific CAR of Embodiment 1 or 2, wherein V<sub>L2</sub> is located at the N-terminus of V<sub>H2</sub>.

Embodiment 5. The bispecific CAR of Embodiment 1 or 2, wherein V<sub>H1</sub> is located at the N-terminus of V<sub>L1</sub>.

Embodiment 6. The bispecific CAR of Embodiment 1 or 2, wherein V<sub>H2</sub> is located at the N-terminus of V<sub>L2</sub>.

Embodiment 7. The bispecific CAR of any of Embodiments 1-6, wherein V<sub>L1</sub> and V<sub>H1</sub> 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.

Embodiment 8. The bispecific CAR of any of Embodiment 1-7, wherein V<sub>L2</sub> and V<sub>H2</sub> 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.

Embodiment 9. The bispecific CAR of any of Embodiments 1-8, 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.

Embodiment 10. The bispecific CAR of any of Embodiments 1-9, 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.

Embodiment 11. The bispecific CAR of Embodiment 10, 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.

Embodiment 12. The bispecific CAR of Embodiment 10 or 11, wherein the cytoplasmic signaling domain comprises a cytoplasmic signaling domain of CD3 $\zeta$ .

Embodiment 13. The bispecific CAR of any of Embodiments 10-12, wherein the hinge region comprises a hinge region of IgG4, CD8, CD28, CD137, or combinations thereof.

Embodiment 14. The bispecific CAR of any of Embodiments 10-13, wherein the transmembrane domain comprises a transmembrane domain of CD8, CD28, CD3 $\epsilon$ , CD45, CD4, CD5, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137, CD154, or combinations thereof.

Embodiment 15. The bispecific CAR of any of Embodiments 1-14, 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.

Embodiment 16. An immune cell expressing the bispecific CAR of any of Embodiments 1-15.

Embodiment 17. The immune cell of Embodiment 16, wherein the immune cell is a T cell or a natural killer (NK) cell.

Embodiment 18. A nucleic acid encoding the bispecific CAR of any of Embodiments 1-15.

Embodiment 19. A vector comprising the nucleic acid of Embodiment 18.

Embodiment 20. A pharmaceutical composition, comprising the bispecific CAR of any of Embodiments 1-15, the immune cell of Embodiment 16 or 17, the nucleic acid of Embodiment 18, or the vector of Embodiment 19.

Embodiment 21. A method of treating an autoimmune disorder, the method comprising administering the immune cell of Embodiment 16 or 17, or the pharmaceutical composition of Embodiment 20, to a subject in need thereof.

Embodiment 22. The method of Embodiment 21, wherein the autoimmune disorder is systemic lupus erythematosus (SLE), systemic sclerosis, inflammatory myopathy, systemic scleroderma, multiple sclerosis, myasthenia gravis, a myositis autoantibody-driven disease, or

neuromyelitis optica.

Embodiment 23. The method of Embodiment 22, wherein the inflammatory myopathy is polymyositis, dermatomyositis, or inclusion-body myositis.

Embodiment 24. The method of Embodiment 22, wherein the SLE is lupus nephritis.

Embodiment 25. A method of treating a cancer, the method comprising administering the immune cell of Embodiment 16 or 17, or the pharmaceutical composition of Embodiment 20, to a subject in need thereof.

Embodiment 26. The method of Embodiment 25, wherein the cancer is a hematologic cancer.

Embodiment 27. The method of Embodiment 25, wherein the cancer is a B-cell malignancy.

Embodiment 28. The method of Embodiment 25, wherein the cancer is Hodgkin's lymphoma, non-Hodgkin's lymphoma, leukemia, and/or multiple myeloma.

Embodiment 29. The method of Embodiment 25, wherein the cancer is 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.

Embodiment 30. The method of any of Embodiments 21-29, wherein the immune cell is allogeneic or autologous.

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.

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### **Example 1 Construction of anti-CD20/BCMA CARs**

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: 10 TOB1-4 and TOBL1-4, where TOBL1 is C-CAR168 (Figure 1).

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 Reptonectin (TAKARA). The medium was 15 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.

Figure 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***

Antigen-specific activation of the anti-CD20/BCMA CAR-T was evaluated by assaying IFN- $\gamma$  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.

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.

IFN $\gamma$  release was assayed using the CAR-T cells cultured for 7 days.  $1 \times 10^5$  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  $\mu$ l of medium for 18h with an E:T ratio of 1:1. Then the levels of IFN- $\gamma$  secreted in the cell culture supernatant were detected by ELISA.

Expression levels of CD137 were assayed using the CAR-T cells cultured for 7 days.  $1 \times 10^5$  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  $\mu$ l of medium for 18h 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.

The IFN $\gamma$  release results are shown in Figures 3A-3C and Figure 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- $\gamma$ . Similarly, anti-BCMA CAR-T (C-CAR088) cells can specifically recognize BCMA single-positive or CD20/BCMA double-positive target cells to release IFN- $\gamma$ . 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- $\gamma$ . TOB1 to TOB4 CAR-T cells showed high IFN- $\gamma$  release when co-cultured with CD20 positive targets cells, but lower reactivity to BCMA single positive target cells. TOBL1 to TOBL4 CAR-T cells showed high IFN- $\gamma$  release when co-cultured with CD20 positive targets and BCMA positive target cells. TOBL1 to TOBL4 CAR-T cells showed high IFN- $\gamma$  release when co-cultured with target cells naturally expressing CD20 and BCMA.

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 (Figures 4A and 4B).

### **Example 3 Cytotoxicity of anti-CD20/BCMA CAR-T cells *in vitro***

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.

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 (Figures 5A-5B, Figure 6C). Their killing ability was comparable to the anti-CD20 and anti-BCMA monospecific CAR-T cells, with all being dose-dependent (Figures 5A-5B, Figure 6C). The TOBL1 to TOBL4 CAR-T cells (Figure 5B) showed high cytotoxicity to CD20-positive and BCMA-positive target cells. The TOB1 to TOB4 CAR-T cells (Figure 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***

Recent studies have shown that in patients with systemic lupus erythematosus (SLE), the proportion of CD11c<sup>hi</sup>T-bet<sup>+</sup> B cell subsets is significantly increased, and is closely related to the production of autoantibodies and the patient's clinical manifestations. Autoantibodies are

5 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 CD11c<sup>hi</sup>T-bet<sup>+</sup> 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<sup>+</sup> 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).

10 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.

15 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 (Figures 20 7A-7C).

25 C-CAR168 can target both CD20<sup>+</sup> B cells and BCMA<sup>+</sup> 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.

### 30 *In vitro* ABC differentiation

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 PBMC 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 $\mu$ l 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- $\gamma$  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

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<sup>+</sup> cells. The cytolysis of B cells was calculated by the following formula: Percentage of lysis (%) = (1 - (viable CD19<sup>+</sup> cell fraction of the C-CAR168 coculture / viable CD19<sup>+</sup> cell fraction of UT coculture))  $\times$  100. See, Lin et al., Preclinical evaluation of CD8<sup>+</sup> anti-BCMA mRNA CAR T-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

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).

6-8 weeks female B-NDG mice were subcutaneously inoculated with A549-CD20 (CD20<sup>+</sup>) or MM.1S (BCMA<sup>+</sup>) cells. When the average tumor volume reached 100 mm<sup>3</sup>, C-CAR168 CAR-T cells were administered via the tail vein at the dosage of 3~5 $\times$ 10<sup>6</sup> 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*.

Specifically, female B-NDG (NOD.Cg-Prkdc<sup>scid</sup> Il2rg<sup>tm1Vst/Vst</sup>) mice were subcutaneously inoculated with 5  $\times$  10<sup>6</sup> A549-CD20 cells/animal. When the average tumor

5 volume reached about 100 mm<sup>3</sup>, 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 (3×10<sup>6</sup> 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 mm<sup>3</sup> 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 mm<sup>3</sup> (Figure 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) (Figure 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*.

15 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<sup>scid</sup>Il2rg<sup>tm1</sup>/Bcgen) mice were subcutaneously inoculated with 5 ×10<sup>6</sup> MM.1S cells/animal. When the average tumor volume reached about 100 mm<sup>3</sup>, 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<sup>6</sup> CAR-T cells/animal. After administration, the average tumor volume in the vehicle control group continued to increase, reaching 2220.86 ± 117.35 mm<sup>3</sup> on Day 28, with a tumor weight of 2.409 ± 0.216 g. The average tumor volumes in the C-CAR168-1 and C-CAR168-2 groups began to decrease from Day 10 (Figure 9B, left panel). By Day 28, the average tumor volumes were 109.2 ± 88.92 mm<sup>3</sup> and 9.07 ± 5.58 mm<sup>3</sup>, respectively, and the tumor weights were 0.041 ± 0.034 g and 0.003 ± 0.002 g, respectively (Figure 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<sup>6</sup> 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

To evaluate the *in vivo* anti-tumor effects of C-CAR168, 65 female B-NDG (NOD.CB17- *Prkdc<sup>scid</sup>Il2rg<sup>tm1</sup>* /Bcgen) mice were subcutaneous inoculated with  $1 \times 10^6$  K562-CD20-BCMA cells/animal. When the average tumor volume reached about  $100 \text{mm}^3$ , 50 animals were selected and randomly divided into 5 groups: vehicle control group, T cell control group, C-CAR168 low-dose group ( $1 \times 10^6$  CAR-T cells/mouse), medium-dose group ( $5 \times 10^6$  CAR-T cells/mouse) and high-dose group ( $10 \times 10^6$  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.

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  $2628.78 \pm 117.32 \text{mm}^3$  and  $2536.23 \pm 97.80 \text{mm}^3$ , 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 (Figure 9E). Figure 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.

In summary, a single intravenous administration of  $1 \times 10^6$ ,  $5 \times 10^6$  or  $10 \times 10^6$  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

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.

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.

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  $\mu\text{g}/\text{mL}$  to the HEK293T cell array transiently transfected with 5220 membrane proteins. Flow cytometry results show that C-CAR168 scFv-RabFc bound strongly to human CD20 and BCMA (Figure 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 (Figure 8B). In addition to CD20 and BCMA, C-CAR168 scFv-RabFc showed specific binding to FCGR1A (Figure 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  $\mu\text{g}/\text{mL}$  and 5  $\mu\text{g}/\text{mL}$ , 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.

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- $\gamma$ , TNF- $\alpha$ , 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.

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”) (Figure 8D, left panel), indicating that C-CAR168 does not bind specifically to ITGB2-ITGAM or ITGB2-ITGAL *in vitro*.

5 Cytokines in the cell culture supernatant were assayed, and the results showed that C-CAR168 CAR-T cells secreted high levels of IFN- $\gamma$  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- $\gamma$  in the supernatant did not increase significantly (Figure 8D, right panel). The results further showed that C-CAR168 did not specifically recognize ITGB2-ITGAM and ITGB2-ITGAL *in vitro*.

10 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.

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### **Example 7 C-CAR168 shows robust potency against autologous B cells from SLE patients**

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.

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#### Efficiency of C-CAR168 to eliminate pan B cells from lupus patients *in vitro*

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 heterogenous nature of lupus patients. Patients who recently received B cell depleting antibodies were excluded.

25

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 (Figure 10A).

30

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- $\gamma$  levels. Result from one representative sample of 8 patients is shown in Figure 10B. Thus, C-CAR168 cells generated from SLE patient samples showed robust activity against target cells expressing CD20 and BCMA.

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- $\gamma$  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 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))  $\times$  100. Results from one representative sample of 8 patients are shown in Figures 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*

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

Blood samples or PBMCs from lupus patients will be processed for ABCs differentiation and CAR-T production as well as functional analysis.

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*

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<sup>+</sup> 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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The structures of the anti-CD20/BCMA CARs, TOB1-4 and TOBL1-4, are shown in

Table 1.

**Table 1**

Anti-CD20/BCMA CAR	scFv V <sub>H</sub> /V <sub>L</sub> order	CAR structure

TN-OF-B20-L1 (TOBL1, or C-CAR168)	OF(V <sub>L</sub> -V <sub>H</sub> ) – B20(V <sub>L</sub> -V <sub>H</sub> )	SP – OF V <sub>L</sub> – linker 1 – OF V <sub>H</sub> – linker 2 – B20 V <sub>L</sub> – linker 3 – B20V <sub>H</sub> – CD8 hinge – CD8 TM – 41BB – CD3z
TN-OF-B20-L2 (TOBL2)	OF(V <sub>H</sub> -V <sub>L</sub> ) – B20(V <sub>L</sub> -V <sub>H</sub> )	SP – OF V <sub>H</sub> – linker 1 – OF V <sub>L</sub> – linker 2 – B20 V <sub>L</sub> – linker 3 – B20V <sub>H</sub> – CD8 hinge – CD8 TM – 41BB – CD3z
TN-OF-B20-L3 (TOBL3)	OF(V <sub>H</sub> -V <sub>L</sub> ) – B20(V <sub>H</sub> -V <sub>L</sub> )	SP – OF V <sub>H</sub> – linker 1 – OF V <sub>L</sub> – linker 2 – B20 V <sub>H</sub> – linker 3 – B20V <sub>L</sub> – CD8 hinge – CD8 TM – 41BB – CD3z
TN-OF-B20-L4 (TOBL4)	OF(V <sub>L</sub> -V <sub>H</sub> ) – B20(V <sub>H</sub> -V <sub>L</sub> )	SP – OF V <sub>L</sub> – linker 1 – OF V <sub>H</sub> – linker 2 – B20 V <sub>H</sub> – linker 3 – B20V <sub>L</sub> – CD8 hinge – CD8 TM – 41BB – CD3z
TN-OF-B20-1 (TOB1)	OF(V <sub>L</sub> -V <sub>H</sub> ) – B20(V <sub>H</sub> -V <sub>L</sub> )	SP – OF V <sub>L</sub> – linker 1 – OF V <sub>H</sub> – linker 2 – B20 V <sub>H</sub> – linker 3 – B20V <sub>L</sub> – IgG4 hinge – CD28 TM – 41BB – CD3z
TN-OF-B20-2 (TOB2)	OF(V <sub>L</sub> -V <sub>H</sub> ) – B20(V <sub>L</sub> -V <sub>H</sub> )	SP – OF V <sub>L</sub> – linker 1 – OF V <sub>H</sub> – linker 2 – B20 V <sub>L</sub> – linker 3 – B20V <sub>H</sub> – IgG4 hinge – CD28 TM – 41BB – CD3z
TN-OF-B20-3 (TOB3)	OF(V <sub>H</sub> -V <sub>L</sub> ) – B20(V <sub>L</sub> -V <sub>H</sub> )	SP – OF V <sub>H</sub> – linker 1 – OF V <sub>L</sub> – linker 2 – B20 V <sub>L</sub> – linker 3 – B20V <sub>H</sub> – IgG4 hinge – CD28 TM – 41BB – CD3z
TN-OF-B20-4 (TOB4)	OF(V <sub>H</sub> -V <sub>L</sub> ) – B20(V <sub>H</sub> -V <sub>L</sub> )	SP – OF V <sub>H</sub> – linker 1 – OF V <sub>L</sub> – linker 2 – B20 V <sub>H</sub> – linker 3 – B20V <sub>L</sub> – IgG4 hinge – CD28 TM – 41BB – CD3z

Sequences:

**TN-OF-B20-L1 (TOBL1, or C-CAR168)**

CD8a SP nucleic acid sequence (63nt)

5 atggccttaccagtgaccgcttgctcctgccgctggccttgctgctccacgcccaggccg (SEQ ID NO:1)

CD8a SP amino acid sequence:

**MALPVTALLLPLALLLHAARP** (SEQ ID NO:2)

10 OF V<sub>L</sub> nucleic acid sequence (321nt)

GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCTCCAGGGGAAAGAG  
 CCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAGCTACTTAGCCTGGTACCA  
 ACAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGATGCATCCAACAGGGC  
 CACTGGCATCCCAGCCAGGTTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTC  
 15 ACCATCAGCAGCCTAGAGCCTGAAGATTTTGCAGTTTATTACTGTCAGCAGCGTA  
 GCAACTGGCCGATCACCTTCGGCCAAGGGACACGACTGGAGATTAAA (SEQ ID  
 NO:3)



ctccaactacctgaactggtaccagcagaagccccgcaaggcccccaagcccctgatctactacacctccaacctgcagtcggcgt  
 gccctcccgggttctccggctccggctccggcaccgactacacctgacctctcctcctgcagcccaggacttcgccacctactac  
 tgcattggccagaccatctcctctacacctcggccagggcaccagaagctggagatcaag (SEQ ID NO:11)

5 B20 V<sub>L</sub> amino acid sequence:

**DIQMTQSPSSLSASVGDRTITCRASQGISNYLNWYQQKPGKAPKPLIYYTSNLQ  
 SGVPSRFRSGSGSGTDYTLTISSLQPEDFATYYCMGQTISSYTFGQGKLEIK** (SEQ  
 ID NO:12)

10 Linker-3 nucleic acid sequence (45 nt)

Ggtggcgggtgctcgggcgggtggtgggtcgggtggcggcgatct (SEQ ID NO:13)

Linker-3 amino acid sequence:

**GGGGSGGGGSGGGGS** (SEQ ID NO:14)

15

B20 V<sub>H</sub> nucleic acid sequence (363nt)

Gaggtgcagctggtggagtccggcggcgccctggtgcagcccggcggtcctgcgggtgtcctgcgccgctccggcttcacctt  
 ctccaacttcgacatggcctgggtgcggcaggccccggcaagggcctggtgtgggtgtcctccatcaccaccggcggcaccag  
 ccattctacgccgactccgtgaagggcgggtaccatctccgggacaacccaagaacacctgtacctgcagatgaactccctgc  
 20 gggccgaggacaccgccgtgtactactgcgtcggcaccggctactacgacggctaccacctgttcgactactggggccagggcacc  
 ctggtgaccgtgtcctcc (SEQ ID NO:15)

B20 V<sub>H</sub> amino acid sequence:

25 **EVQLVESGGGLVQPGGSLRLSCAASGFTFSNFDMAWVRQAPGKGLVWVSSITT  
 GADHAIYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCVRHGYDGYH  
 LFDYWGQGTLVTVSS** (SEQ ID NO:16)

CD8a hinge nucleic acid sequence (165nt)

30 Ttcgtccgggttctcctgccagcgaagcccaccagcagccagcggcggcaccaccaacaccggcggccaccatcgctcgcag  
 cccctgtcctcgcggcagaggcgtgccggccagcggcggggggcgcagtgacacaggggggctggacttcgctgtgat  
 (SEQ ID NO:17)

CD8a hinge amino acid sequence:

**FVPVFLPAKPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACD**

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(SEQ ID NO:18)

CD8a TM nucleic acid sequence (72nt)

Atctacatctgggcgcccttggccgggacttgtggggtccttctctctgtcactggttatcacccttactgc (SEQ ID NO:19)

CD8a TM amino acid sequence:

**IYIWAPLAGTCGVLLLSLVITLYC** (SEQ ID NO:20)

4-1BB nucleic acid sequence (126nt)

Aaacggggcagaaagaaactcctgtatatattcaacaaccatttatgagaccagtacaaactactcaagaggaagatggctgtagct  
gccgattccagaagaagaagaaggaggatgtgaactg (SEQ ID NO:21)

4-1BB amino acid sequence:

**KRGRKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCEL** (SEQ ID NO:22)

CD3z nucleic acid sequence (336nt)

Agagtgaagttcagcaggagcgcagacgccccgcgtaccagcagggccagaaccagctctataacgagctcaatctaggacga  
agagaggagtacgatgttttgacaagagacgtggccgggaccctgagatggggggaaagccgagaaggaagaaccctcaggaa  
ggcctgtacaatgaactgcagaaagataagatggcggaggcctacagtgagattgggatgaaaggcgagcgcggagggggcaag  
gggcacgatggccttaccaggtctcagtagaccaccaaggacacctacagcgccttcacatgcaggccctgccccctcgctaa  
(SEQ ID NO:23)

CD3z amino acid sequence:

**RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLKRRGRDPEMGGKPRRK  
NPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDLGLYQGLSTATKDTYDAL  
HMQALPPR** (SEQ ID NO:24)

TOBL1 nucleic acid sequence (2247nt)

atggccttaccagtgaccgacctgtctctgccgctggccttctgtctccacgccagccgGAAATTGTGTTGACA  
CAGTCTCCAGCCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCA  
GGGCCAGTCAGAGTGTTAGCAGCTACTTAGCCTGGTACCAACAGAAACCTGGCC  
AGGCTCCCAGGCTCCTCATCTATGATGCATCCAACAGGGCCACTGGCATCCCAGC  
CAGGTTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGCAGCCTA  
GAGCCTGAAGATTTTGCAGTTTATTACTGTCAGCAGCGTAGCAACTGGCCGATCA

CCTTCGGCCAAGGGACACGACTGGAGATTAAGGCAGTACTAGCGGTGGTGGCT  
 CCGGGGGCGGTTCCGGTGGGGGCGGCAGCAGCGAAGTGCAGCTGGTGGAGTCTG  
 GGGGAGGCTTGGTACAGCCTGGCAGGTCCCTGAGACTCTCCTGTGCAGCCTCTGG  
 ATTCACCTTTAATGATTATGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGC  
 5 CTGGAGTGGGTCTCAACTATTAGTTGGAATAGTGGTTCCATAGGCTATGCGGACT  
 CTGTGAAGGGCCGATTACCATCTCCAGAGACAACGCCAAGAAGTCCCTGTATCT  
 GCAAATGAACAGTCTGAGAGCTGAGGACACGGCCTTGTATTACTGTGCAAAAGA  
 TATACAGTACGGCAACTACTACTACGGTATGGACGTCTGGGGCCAAGGGACCAC  
 GGTCACCGTCTCCTCAGGAGGTGGTGGATCCGacatccagatgaccagtccccctcctcctgtccgc  
 10 ctccgtgggcgaccgggtgacatcacctgccgggctcccagggcatctccaactacctgaactggtaccagcagaagcccggca  
 aggcccccaagcccctgatctactacacctccaactgcagtccggcgtgcctcccggttctccggctccggctccggcaccgact  
 acacctgacatctcctcctgcagcccaggacttgcacactactactgcatggccagaccatctcctctacacctggccag  
 ggcaccaagctggagatcaagGgtggcgggtggctcgggcggtggtgggtcgggtggcggcgatctgaggtgcagctggtgga  
 gtccggcggcgccctggtgcagcccggcggtcctcctgcggctgtcctgcgccgctcggcttcacttctccaacttcgacatggc  
 15 ctgggtgcggcaggccccggcaaggcctggtgtgggtgtcctcatcaccaccggcggcaccagccatctacgccgactcc  
 gtgaaggccggttaccatctcccgggacaacgccaagaacacctgtacctgcagatgaactcctcggggccaggacaccg  
 ccgtgtactactgctgcggcacggctactacgacggctaccacctgttcgactactggggccagggcacctggtgaccgtgtcctc  
 ctctgtccggtctcctgcccagcgaagcccaccagcagccagcggcggcggggcgagtgacacaggggggctggacttcgctgtgatct  
 20 acatctggggcgcccttggccgggacttgggggtccttctcctgtcactggttatcacccttactgcaaacggggcagaagaagaactc  
 ctgtatatattcaacaaccatttatgagaccagtacaaactactcaagaggaagatggctgtagctgccgattccagaagaaga  
 aggaggatgtgaactgagagtgaagttcagcaggagcgcagacgccccgcgtaccagcagggccagaaccagctctataacga  
 gctcaatctaggacgaagagaggagtacgatgttttgacaagagacgtggccgggaccctgagatggggggaaagccgagaag  
 gaagaacctcaggaaggcctgtacaatgaactgcagaaagataagatggcggaggcctacagtgagattgggatgaaaggcgag  
 25 cgccggaggggcaaggggcacgatggccttaccagggtctcagtacagccaccaaggacacctacgacgcccttccatgcagg  
 cctgccccctcgctaa (SEQ ID NO:25)

**TOBL1** amino acid sequence:

MALPVTALLLPLALLHAARPEIVLTQSPATLSLSPGERATLSCRASQSVSSYLA  
 30 WYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQ  
 QRSNWPITFGQGRLEIKGSTSGGSGGGSGGGSSSEVQLVESGGGLVQPGRSL  
 RLSCAASGFTFNDYAMHWVRQAPGKGLEWVSTISWNSGSIGYADSVKGRFTISR  
 DNAKKSLLYQMNSLRAEDTALYYCAKDIQYGNYYYGMDVWGQGTITVTVSSGG  
 GGSDIQMTQSPSSLSASVGDRTITCRASQGISNYLNWYQQKPGKAPKPLIYYTS

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NLQSGVPSRFSGSGSGTDYTLTISSLQPEDFATYYCMGQTISSYTFGQGTKLEIK  
GGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFSNFDMAWV  
RQAPGKGLVWVSSITTGADHAIYADSVKGRFTISRDNKNTLYLQMNSLRAEDT  
AVYYCVRHGYDGYHFLFDYWGGQTLVTVSSFVPVFLPAKPTTTPAPRPPTPAPT  
IASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYC  
KRGRKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPA  
YQQGQNQLYNELNLGRREEYDVLDKRRGRDPENGGKPRRKNPQEGLYNELQ  
KDKMAEAYSEIGMKGERRRGKGHGHDGLYQGLSTATKDTYDALHMQALPPR

(SEQ ID NO:26)

*TN-OF-B20-L2 (TOBL2)*

CD8a SP nucleic acid sequence (63nt)

Atggcctaccagtgaccgcttgctcctgccgctggccttgctcctccagccgagccg (SEQ ID NO:27)

OF V<sub>H</sub> nucleic acid sequence

GAAGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTCCCTG  
AGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAATGATTATGCCATGCACTGGG  
TCCGGCAAGCTCCAGGGAAGGGCCTGGAGTGGGTCTCAACTATTAGTTGGAATA  
GTGGTTCCATAGGCTATGCGGACTCTGTGAAGGGCCGATTACCATCTCCAGAGA  
CAACGCCAAGAAGTCCCTGTATCTGCAAATGAACAGTCTGAGAGCTGAGGACAC  
GGCCTTGTATTACTGTGCAAAAGATATACAGTACGGCAACTACTACTACGGTATG  
GACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA (SEQ ID NO:28)

Linker-1 nucleic acid sequence

GGCAGTACTAGCGGTGGTGGCTCCGGGGGCGGTTCCGGTGGGGGCGGCAGCAGC  
(SEQ ID NO:29)

OF V<sub>L</sub> nucleic acid sequence

GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCTCCAGGGGAAAGAG  
CCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAGCTACTTAGCCTGGTACCA  
ACAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGATGCATCCAACAGGGC  
CACTGGCATCCCAGCCAGGTTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTC  
ACCATCAGCAGCCTAGAGCCTGAAGATTTTGCAGTTTATTACTGTCAGCAGCGTA  
GCAACTGGCCGATCACCTTCGGCCAAGGGACACGACTGGAGATTA (SEQ ID

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NO:30)

Linker-2 nucleic acid sequence

GGAGGTGGTGGATCC (SEQ ID NO:31)

BCMA-20 scFv (729nt):

B20 V<sub>L</sub> nucleic acid sequence (321nt)

gacatccagatgaccagtcctccctctccctgtccgcctcctggggcgaccgggtgaccatcacctgccggcctcccagggcatc  
tccaactactgaaactggtaccagcagaagcccggcaaggcccccaagcccctgatctactacacctccaacctgcagtcggcgtg  
ccctcccgttctccggctccggctccggcaccgactacaccctgaccatctcctcctgcagcccaggacttcgccactactact  
gcatgggccagaccatctcctctacaccttcggccagggcaccaagctggagatcaag (SEQ ID NO:32)

Linker-3 nucleic acid sequence (45 nt)

ggtggcggtggctcgggcgggtgggtcgggtggcgggcgatct (SEQ ID NO:33)

B20 V<sub>H</sub> nucleic acid sequence (363nt)

gaggtgcagctggtggagtccggcggcggcctggtgcagcccggcggctccctgcggctgtcctgcgccgctccggctcacctt  
ctccaacttcgacatggcctgggtgcggcaggccccggcaagggcctggtgtgggtgtcctccatcaccaccggcggcggcaccag  
ccatctacgccgactccgtgaagggcgggtaccatctcccgggacaacccaagaacacctgtacctgcagatgaactcctgc  
gggccgaggacaccgccgtgtactactgcgtcggcaccggctactacgacggctaccacctgttcgactactggggccagggcacc  
ctggtgaccgtgtcctcc (SEQ ID NO:34)

CD8a hinge nucleic acid sequence (165nt)

Ttcgtgccggttctctgccagcgaagcccaccacgacgccagcggcggcaccaccaacaccggcggccaccatcgcgctgcag  
ccctgtcctctgcgccagaggcgtgccggcagcggcggggggcgcagtgacacgagggggctggacttcgctgtgat  
(SEQ ID NO:35)

CD8a TM nucleic acid sequence (72nt)

Atctacatctgggcgcccttggccgggacttgggggtccttctcctgtcactggttatcacccttactgc (SEQ ID NO:36)

4-1BB nucleic acid sequence (126nt)

Aaacggggcagaaagaactcctgtatatattcaacaaccattatgagaccagtacaaactactcaagaggaagatggctgtagct  
gccgattccagaagaagaagaggatgtgaactg (SEQ ID NO:37)

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CD3z nucleic acid sequence (336nt)

Agagtgaagttcagcaggagcgcagacgccccgcgtaccagcagggccagaaccagctctataacgagctcaatctaggacga  
agagaggagtacgatgtttggacaagagacgtggccggaccctgagatggggggaaagccgagaaggaagaaccctcaggaa  
ggcctgtacaatgaactgcagaaagataagatggcggaggcctacagtgagattgggatgaaaggcgagcgcggaggggcaag  
5 gggcacgatggcctttaccaggtctcagtacgccaccaaggacacctacgacgccttcacatgcaggccctgccccctcgctaa  
(SEQ ID NO:38)

**TOBL2** nucleic acid sequence (2247nt)

atggccttaccagtaccgccttgctcctgcccgtggccttgctgctccacgcccaggccgGAAGTGCAGCTGGTG  
10 GAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTCCCTGAGACTCTCCTGTGCA  
GCCTCTGGATTACCTTTAATGATTATGCCATGCACTGGGTCCGGCAAGCTCCAG  
GGAAGGGCCTGGAGTGGGTCTCAACTATTAGTTGGAATAGTGGTTCCATAGGCTA  
TGCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAAGTC  
CCTGTATCTGCAAATGAACAGTCTGAGAGCTGAGGACACGGCCTTGTATTACTGT  
15 GCAAAAGATATACAGTACGGCAACTACTACTACGGTATGGACGTCTGGGGCCAA  
GGGACCACGGTCACCGTCTCCTCAGGCAGTACTAGCGGTGGTGGCTCCGGGGGC  
GGTTCCGGTGGGGGCGGCAGCAGCGAAATTGTGTTGACACAGTCTCCAGCCACC  
CTGTCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTG  
TTAGCAGCTACTTAGCCTGGTACCAACAGAAACCTGGCCAGGCTCCCAGGCTCCT  
20 CATCTATGATGCATCCAACAGGGCCACTGGCATCCCAGCCAGGTTTCAGTGGCAGT  
GGGTCTGGGACAGACTTCACTCTCACCATCAGCAGCCTAGAGCCTGAAGATTTTG  
CAGTTTATTACTGTCAGCAGCGTAGCAACTGGCCGATCACCTTCGGCCAAGGGAC  
ACGACTGGAGATTAAAGGAGGTGGTGGATCCGacatccagatgaccagtcctccctcctcctgtccg  
cctccgtgggcgaccgggtgaccatcacctgcccggcctcccagggcctccaactacctgaactggtaccagcagaagcccggc  
25 aaggccccaagcccctgatctactacacctccaacctgcagtccggcgtgcctcccggttctccggctccggctccggcaccgac  
tacacctgaccatctcctcctgcagcccaggacttcgccactactactgcattgggcccagaccatctcctctacaccttcggcca  
gggcaccaagctggagatcaagGgtggcgggtggctcggcggtgggtgggctgggctggcggggatctgaggtgcagctgggtg  
agtccggcggcggcctggtgcagcccggcggctccctgcggctgtcctgcgccgctccggcttcaccttccaacttcgacatgg  
cctgggtgcggcaggccccggcaaggcctggtgtgggtgtcctcaccaccggcgccgaccacgccatctacgccgactc  
30 cgtgaaggccgggtcaccatctcccgggacaacgccaagaacacctgtacctgcagatgaactcctgcggggccgaggacacc  
ggcgtgtactactgcgtgcggcacggctactacgacggctaccacctgttcgactactggggccagggcaccctggtgaccgtgtcct  
ccttcgtcccgttctcctgccagcgaagcccaccacgacgccagcggcgaccaccaacaccggcgcccaccatcgcgtcga  
gccccgtcctgcgcccagaggcgtgccggccagcggcgggggggcgcagtgcacacgagggggctggacttcgctgtgat  
ctacatctgggcgcccctggccgggacttgggggtccttctcctgtcactggttatcccttactgcaaacggggcagaaagaact

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cctgtatatattcaacaaccatttatgagaccagtacaaactactcaagaggaagatggctgtagctgccgattccagaagaagaag  
aaggaggatgtgaactgAgagtgaagttcagcaggagcgcagacgcccccgctaccagcagggccagaaccagctctataacg  
agctcaatctaggacgaagagaggagtacgatgttttgacaagagacgtggccgggaccctgagatgggggggaaagccgagaag  
gaagaaccctcaggaaggcctgtacaatgaactgcagaaagataagatggcggaggcctacagtgagattgggatgaaaggcgag  
5 cgccggaggggcaaggggcacgatggcctttaccaggggtctcagtacagccaccaaggacacctacgacgcccttcacatgcagg  
ccctgccccctcgetaa (SEQ ID NO:39)

TOBL2 amino acid sequence:

MALPVTALLLPLALLHAARPEVQLVESGGGLVQPGRSLRLSCAASGFTFNDYA  
10 MHWVRQAPGKGLEWVSTISWNSGSIGYADSVKGRFTISRDNAAKSLYLQMNSL  
RAEDTALYYCAKDIQYGNYYYGMDVWGQGTTVTVSSGSTSGGGSGGGSGGGG  
SSEIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNR  
ATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPITFGQGRLEIKGG  
GGSDIQMTQSPSSLSASVGDRTITCRASQGISNYLNWYQQKPGKAPKPLIYYTS  
15 NLQSGVPSRFSGSGSGTDYTLTISSLQPEDFATYYCMGQTISSYTFGQGTKLEIK  
GGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFSNFDMAWV  
RQAPGKGLVWVSSITGADHAIYADSVKGRFTISRDNAAKNTLYLQMNSLRAEDT  
AVYYCVRHGYDGYHFLFDYWGQGLVTVSSFVPVFLPAKPTTTPAPRPPTPAPT  
IASQPLSLRPEACRPAAGGAVHTRGLDFACDIYWAPLAGTCVLLLSLVITLYC  
20 KRGRKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEEGGCELRVKFSRSADAPA  
YQQGQNQLYNELNLGRREEYDVLDKRRGRDPENGGKPRRKNPQEGLYNELQ  
KDKMAEAYSEIGMKGERRRGKGHGDLQGLSTATKDTYDALHMQUALPPR  
(SEQ ID NO:40)

TN-OF-B20-L3 (TOBL3)

CD8a SP (63nt) nucleic acid sequence

Atggccttaccagtgaccgccttgctcctgccgctggccttgctgctccacgccgcccaggccg (SEQ ID NO:41)

OF V<sub>H</sub> nucleic acid sequence

30 GAAGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTCCCTG  
AGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAATGATTATGCCATGCACTGGG  
TCCGGCAAGCTCCAGGGAAGGGCCTGGAGTGGGTCTCAACTATTAGTTGGAATA  
GTGGTTCCATAGGCTATGCGGACTCTGTGAAGGGCCGATTACCATCTCCAGAGA  
CAACGCCAAGAAGTCCCTGTATCTGCAAATGAACAGTCTGAGAGCTGAGGACAC

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GGCCTTGTATTACTGTGCAAAAAGATATACAGTACGGCAACTACTACTACGGTATG  
GACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA (SEQ ID NO:42)

Linker-1 nucleic acid sequence

GGCAGTACTAGCGGTGGTGGCTCCGGGGGCGGTTCCGGTGGGGGCGGCAGCAGC  
(SEQ ID NO:43)

OF V<sub>L</sub> nucleic acid sequence

GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCTCCAGGGGAAAGAG  
CCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAGCTACTTAGCCTGGTACCA  
ACAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGATGCATCCAACAGGGC  
CACTGGCATCCCAGCCAGGTTCCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTC  
ACCATCAGCAGCCTAGAGCCTGAAGATTTTGCAGTTTATTACTGTCAGCAGCGTA  
GCAACTGGCCGATCACCTTCGGCCAAGGGACACGACTGGAGATTAAA (SEQ ID  
NO:44)

Linker-2 nucleic acid sequence

GGAGGTGGTGGATCC (SEQ ID NO:45)

BCMA-20 scFv (729nt):

B20 V<sub>H</sub> nucleic acid sequence (363nt)

Gaggtgcagctggtggagtcggcgggcgccctggtgcagccggcggtccctgcggtgtcctgcccgcctccggttcacctt  
ctccaacttcgacatggcctgggtgcccaggccccggcaagggcctggtgtgggtgtcctccatcaccaccggcgccgaccagc  
ccatctacggcgactccgtgaagggccggttcaccatctcccgggacaacccaagaacacctgtacctgcagatgaactccctgc  
gggcccaggacaccgcccgtgtactactgcgtgcccacggctactacgagctaccacctgttcgactactggggccagggcacc  
ctggtgaccgtgtcctcc (SEQ ID NO:46)

Linker-3 nucleic acid sequence (45 nt)

Ggtggcggtggtcggcggtggtgggtcgggtggcgcgatct (SEQ ID NO:47)

B20 V<sub>L</sub> nucleic acid sequence (321nt)

Gacatccagatgaccagtcctcctcctgtccgctccgtggcgaccgggtgaccatcacctgcccggcctcccagggc  
ctccaactacctgaactggtaccagcagaagcccggcaaggcccccaagcccctgatctactacacctccaacctgcagtcggcgt  
gccctcccgttctccgctccggtcggcaccgactacacctgaccatctcctcctgcagcccaggacttcgccactactac

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tgcatgggccagaccatctcctctacaccttcggccaggccaccaagctggagatcaag (SEQ ID NO:48)

CD8a hinge nucleic acid sequence (165nt)

Ttcgtgccggtcttctgccagcgaagcccaccacgacgccagcgcgaccaccaacaccggcgcccaccatcgcgctcgcag  
5 ccctgtccctgcgcccagaggcgtgccggccagcggcggggggcgagtgacacgagggggctggacttcgctgtgat  
(SEQ ID NO:49)

CD8a TM nucleic acid sequence (72nt)

Atctacatctggcgcccttgccgggacttggggtccttctcctgtcactggttatcacctttactgc (SEQ ID NO:50)

4-1BB nucleic acid sequence (126nt)

Aaacggggcagaaagaaactcctgtatatattcaaacaccatttatgagaccagtacaaactactcaagaggaagatggctgtagct  
gccgattccagaagaagaaggaggatgtgaactg (SEQ ID NO:51)

CD3z nucleic acid sequence (336nt)

Agagtgaagttcagcaggagcgcagacgccccgcgtaccagcaggccagaaccagctctataacgagctcaatctaggacga  
agagaggagtacgatgtttggacaagagacgtggccgggaccctgagatggggggaaagccgagaaggaagaaccctcaggaa  
ggcctgtacaatgaactgcagaaagataagatggcggaggcctacagtgagattgggatgaaagggcagcgcggagggggcaag  
gggcacgatggcctttaccagggtctcagtacagccaccaaggacacctacgacgcccttcacatgcaggecctgccccctcgctaa  
20 (SEQ ID NO:52)

**TOBL3** nucleic acid sequence

atggccttaccagtaccgcttgcctctgccgctggccttgcctccacgcccaggccgGAAGTGCAGCTGGTG  
GAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTCCCTGAGACTCTCCTGTGCA  
25 GCCTCTGGATTCACCTTTAATGATTATGCCATGCACTGGGTCCGGCAAGCTCCAG  
GGAAGGGCCTGGAGTGGGTCTCAACTATTAGTTGGAATAGTGGTTCCATAGGCTA  
TGCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAAGTC  
CCTGTATCTGCAAATGAACAGTCTGAGAGCTGAGGACACGGCCTTGTATTACTGT  
GCAAAGATATACAGTACGGCAACTACTACTACGGTATGGACGTCTGGGGCCAA  
30 GGGACCACGGTACCGTCTCCTCAGGCAGTACTAGCGGTGGTGGCTCCGGGGGC  
GGTTCCGGTGGGGGCGGCAGCAGCGAAATTGTGTTGACACAGTCTCCAGCCACC  
CTGTCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTG  
TTAGCAGCTACTTAGCCTGGTACCAACAGAAACCTGGCCAGGCTCCCAGGCTCCT  
CATCTATGATGCATCCAACAGGGCCACTGGCATCCCAGCCAGGTTTCAGTGGCAGT



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**YQQGQNQLYNELNLRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQ  
KDKMAEAYSEIGMKGERRRGKGHDLGLYQGLSTATKDTYDALHMQUALPPR**  
(SEQ ID NO:54)

5 **TN-OF-B20-L4 (TOBL4)**

CD8a SP nucleic acid sequence (63nt)

Atggccttaccagtgaccgccttgctcctgccgctggccttgctgctccacgccgcccaggccg (SEQ ID NO:55)

OF V<sub>L</sub> nucleic acid sequence

10 GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCTCCAGGGGAAAGAG  
CCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAGCTACTTAGCCTGGTACCA  
ACAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGATGCATCCAACAGGGC  
CACTGGCATCCCAGCCAGGTTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTC  
ACCATCAGCAGCCTAGAGCCTGAAGATTTTGCAGTTTATTACTGTCAGCAGCGTA  
15 GCAACTGGCCGATCACCTTCGGCCAAGGGACACGACTGGAGATTAAA (SEQ ID  
NO:56)

Linker-1 nucleic acid sequence

GGCAGTACTAGCGGTGGTGGCTCCGGGGGCGGTTCCGGTGGGGGCGGCAGCAGC  
20 (SEQ ID NO:57)

OF V<sub>H</sub> nucleic acid sequence

GAAGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTCCCTG  
AGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAATGATTATGCCATGCACTGGG  
25 TCCGGCAAGCTCCAGGGAAGGGCCTGGAGTGGGTCTCAACTATTAGTTGGAATA  
GTGGTTCCATAGGCTATGCGGACTCTGTGAAGGGCCGATTACCATCTCCAGAGA  
CAACGCCAAGAAGTCCCTGTATCTGCAAATGAACAGTCTGAGAGCTGAGGACAC  
GGCCTTGTATTACTGTGCAAAAAGATATACAGTACGGCAACTACTACTACGGTATG  
GACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA (SEQ ID NO:58)

30

Linker-2 nucleic acid sequence

GGAGGTGGTGGATCC (SEQ ID NO:59)

BCMA-20 scFv (729nt):

B20 V<sub>H</sub> nucleic acid sequence (363nt)

Gaggtgcagctggtggagtcggcgccggcctggtgcagccggcggtccctgcggctgtcctgcgccgctccggcttcacctt  
 ctccaacttcgacatggcctgggtgcccagggccccggcaagggcctggtgtgggtgtcctccatcaccaccggcgccgaccag  
 ccatctacgccgactccgtgaagggccggtcaccatctcccgggacaacccaagaacacctgtacctgcagatgaactccctgc  
 5 gggccgaggacaccgccgtgtactactgcgtgcccacggctactacagggctaccacctgttcgactactggggccagggcacc  
 ctggtgaccgtgtcctcc (SEQ ID NO:60)

Linker-3 nucleic acid sequence (45 nt)

Ggtggcggtggtcggcggtggtgggtcgggtggcgccggatct (SEQ ID NO:61)

B20 V<sub>L</sub> nucleic acid sequence (321nt)

Gacatccagatgaccagtccccctctcctgtccgctccgtggcgaccgggtgaccatcacctgccgggctcccaggat  
 ctccaactacctgaactggtaccagcagaagcccggcaagggcccccaagcccctgatctactacacctccaactgcagtcggcgt  
 gccctcccgttctccggctccggctccggcaccgactacacctgaccatctcctcctgcagcccaggacttcgccactactac  
 15 tgcattggccagaccatctcctctacaccttcggccaggccaccaagctggagatcaag (SEQ ID NO:62)

CD8a hinge nucleic acid sequence (165nt)

Ttcgtccggttctctgccagcgaagcccaccacgacgccagcgcgcgaccaccaacaccggcgcccaccatcgctcgcag  
 cccctgtccctgcgcccagaggcgtgccggccagcggcgggggcgagtgacacaggggggctggacttcgctgtgat  
 20 (SEQ ID NO:63)

CD8a TM nucleic acid sequence (72nt)

Atctacatctggcgcccttggccgggacttgggggtccttctcctgtcactggttatcacccttactgc (SEQ ID NO:64)

4-1BB nucleic acid sequence (126nt)

Aaacggggcagaaagaactcctgtatatattcaacaaccattatgagaccagtacaaactactcaagaggaagatggctgtagct  
 gccgattccagaagaagaaggaggatgtgaactg (SEQ ID NO:65)

CD3z nucleic acid sequence (336nt)

Agagtgaagttcagcaggagcgcagacgccccgcgtaccagcaggccagaaccagctctataacgagctcaatctaggacga  
 agagaggagtacgatgttttgacaagagacgtggccgggaccctgagatggggggaaagccgagaaggaagaaccctcaggaa  
 ggctgtacaatgaactgcagaaagataagatggcggaggcctacagtgagattgggatgaaaggcgagcgcggagggggcaag  
 gggcacgatggccttaccagggtctcagtacagccaccaaggacacctacgacgcccttcacatgcaggccctgccccctcgctaa  
 30 (SEQ ID NO:66)

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**TOBL4 nucleic acid sequence (2247nt)**

atggccttaccagtgaccgccttgctcctgccgctggccttgctgetccacgcccagggccgGAAATTGTGTTGACA  
CAGTCTCCAGCCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCA  
5 GGGCCAGTCAGAGTGTTAGCAGCTACTTAGCCTGGTACCAACAGAAACCTGGCC  
AGGCTCCCAGGCTCCTCATCTATGATGCATCCAACAGGGCCACTGGCATCCCAGC  
CAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGCAGCCTA  
GAGCCTGAAGATTTTGCAGTTTATTACTGTCAGCAGCGTAGCAACTGGCCGATCA  
CCTTCGGCCAAGGGACACGACTGGAGATTAAAGGCAGTACTAGCGGTGGTGGCT  
10 CCGGGGGCGGTTCCGGTGGGGGCGGCAGCAGCGAAGTGCAGCTGGTGGAGTCTG  
GGGAGGCTTGGTACAGCCTGGCAGGTCCCTGAGACTCTCCTGTGCAGCCTCTGG  
ATTCACCTTTAATGATTATGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGC  
CTGGAGTGGGTCTCAACTATTAGTTGGAATAGTGGTTCATAGGCTATGCGGACT  
CTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAAGTCCCTGTATCT  
15 GCAAATGAACAGTCTGAGAGCTGAGGACACGGCCTTGTATTACTGTGCAAAAGA  
TATACAGTACGGCAACTACTACTACGGTATGGACGTCTGGGGCCAAGGGACCAC  
GGTCACCGTCTCCTCAGGAGGTGGTGGATCCgaggtgcagctggtggagtcggcgggcgccctggtgc  
agccccggcgctccctgcggctgtcctgcgccctccggcttcaccttccaacttcgacatggcctgggtgcggcaggccccg  
gcaagggcctggtgtgggtgtcctccatcaccaccggcgccgaccacgccatctacgccactccgtgaagggccggttcacatct  
20 cccgggacaacgccaagaacaccctgtacctgcagatgaactccctgcgggcccaggacaccgccgtgtactactgcgtgcggca  
cggctactacgaacgctaccacctgttcgactactggggccagggcaccctggtgaccgtgtcctccGgtggcggtggtcggggc  
gtggtgggtcgggtggcgccggtatcGacatccagatgaccagtcctccctcctcctgtccgcctccgtgggcgaccgggtgacc  
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ctacacctcaacctgcagtcggcgtgccctcccggttctccggctccggctccggcaccgactacacctgaccatctcctcctg  
25 cagccccaggacttcgccactactactgcatgggcccagaccatctcctctacaccttcggccagggcaccgaagctggagatcaag  
ttcgtgccggtcttctccagcgaagcccaccacgacgccagcggcgccgaccaccaacaccggcgcccaccatcgcgtgcgagc  
ccctgtccctgcgcccagaggcgtgccggcagcggcgggggggcgagtgacacgaggggggctggacttcgcctgtgatatcta  
catctgggcgcccttggccgggacttgggggtccttctcctgtcactggttatcacccttactgcaaacggggcagaaagaaactcct  
gtatatattcaacaaccatttatgagaccagtacaaactactcaagaggaagatggctgtagctgccgatttcagaagaagaagaag  
30 gaggatgtgaactgAgagtgaagttcagcaggagcgcagacgccccgcgtaccagcagggccagaaccagctctataacgagc  
tcaatctaggacgaagagaggtagatgttttgacaagagacgtggccgggaccctgagatgggggggaaagccgagaaggaa  
gaacctcaggaaggcctgtacaatgaactgcagaaagataagatggcggaggcctacagtgagattgggatgaaaggcgagcgc  
cggaggggcaaggggcacgatggcctttaccagggtctcagtagaccaccaaggacacctacgacgcccttcacatgcaggccct  
gccccctcgctaa (SEQ ID NO:67)

**TOBL4 amino acid sequence:**

MALPVTALLLPLALLLHAARPEIVLTQSPATLSLSPGERATLSCRASQSVSSYLA  
 WYQQKPGQAPRLLIYDASN RATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQ  
 5 QRSNWPITFGQGTRLEIKGSTSGGGSGGGSGGGGSSEVQLVESGGGLVQPGRSL  
 RLSCAASGFTFNDYAMHWVRQAPGKGLEWVSTISWNSGSIGYADSVKGRFTISR  
 DNAKKSLEYLQMNSLRAEDTALYYCAKDIQYGNYYYGMDVWGQGT VTVSSGG  
 GGSEVQLVESGGGLVQP GGSRLRLSCAASGFTFSNFDMAWVRQAPGKGLVWVSS  
 ITTGADHAIYADSVKGRFTISRDN AKNTLYLQMNSLRAEDTAVYYCVRHGYD  
 10 GYHLFDYWGQGT LTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVT  
 ITCRASQGISNYLNWYQQKPGKAPKPLIYYTSNLQSGVPSRFSGSGSGTDYTLTIS  
 SLQPEDFATYYCMGQTISSYTFGQGTKLEIKFVPVFLPAKPTTTPAPRPPTPAPTI  
 ASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYC  
 KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEEGGCELRVKFSRSADAPA  
 15 YQQGQNQLYNELNLGRREEYDVL DKRRGRDPEMGGKPRRKNPQEGLYNELQ  
 KDKMAEAYSEIGMKGERRRGK GHDGLYQGLSTATKDTYDALHMQALPPR  
 (SEQ ID NO:68)

**TN-OF-B20-1(TOB1)**20 **CD8a SP nucleic acid sequence**

ATGGCCTTACCAGTGACCGCCTTGCTCCTGCCGCTGGCCTTGCTGCTCCACGCCG  
 CCAGGCCG (SEQ ID NO:69)

**OF V<sub>L</sub> nucleic acid sequence**

25 GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCTCCAGGGGAAAGAG  
 CCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAGCTACTTAGCCTGGTACCA  
 ACAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGATGCATCCAACAGGGC  
 CACTGGCATCCCAGCCAGGTT CAGTGGCAGTGGGTCTGGGACAGACTTCACTCTC  
 ACCATCAGCAGCCTAGAGCCTGAAGATTTTGCAGTTTATTACTGTCAGCAGCGTA  
 30 GCAACTGGCCGATCACCTTCGGCCAAGGGACACGACTGGAGATTA AA (SEQ ID  
 NO:70)

**Linker-1 nucleic acid sequence**

GGCAGTACTAGCGGTGGTGGCTCCGGGGGCGGTTCCGGTGGGGGCGGCAGCAGC

(SEQ ID NO:71)

OF V<sub>H</sub> nucleic acid sequence

GAAGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTCCCTG  
 5 AGACTCTCCTGTGCAGCCTCTGGATTACCTTTAATGATTATGCCATGCACTGGG  
 TCCGGCAAGCTCCAGGGAAGGGCCTGGAGTGGGTCTCAACTATTAGTTGGAATA  
 GTGGTTCCATAGGCTATGCGGACTCTGTGAAGGGCCGATTACCATCTCCAGAGA  
 CAACGCCAAGAAGTCCCTGTATCTGCAAATGAACAGTCTGAGAGCTGAGGACAC  
 10 GGCCTTGTATTACTGTGCAAAAGATATACAGTACGGCAACTACTACTACGGTATG  
 GACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA (SEQ ID NO:72)

Linker-2 nucleic acid sequence

GGAGGTGGTGGATCC (SEQ ID NO:73)

15 B20 V<sub>H</sub> nucleic acid sequence

Gaggtgcagctggtggagtccggcggcggcctggtgcagcccggcggctcctgcggtgtcctgcgccgcctccggcttcacctt  
 ctccaacttcgacatggcctgggtgcggcaggccccggcaagggcctggtgtgggtgtcctccatcaccaccggcgccgaccacg  
 ccctctacggcactccgtgaagggccggtcaccatctcccgggacaacccaagaacacctgtacctgcagatgaactccctgc  
 20 gggccgaggacaccgcccgtgtactactgcgtgcggcacggctactacgacggctaccacctgttcgactactggggccagggcacc  
 ctggtgaccgtgtcctcc (SEQ ID NO:74)

Linker-3 nucleic acid sequence

ggtggcgggtggctcgggcgggtgggtggcggcgggatct (SEQ ID NO:75)

25 B20 V<sub>L</sub> nucleic acid sequence

Gacatccagatgaccagtcctcctcctgtcgcctccgtggcggcaccgggtgaccatcacctgccggcctcccagggeat  
 ctccaactacctgaactggtaccagcagaagcccggcaagggcccccaagcccctgatctactacacctccaactgcagtcggcgt  
 gcctcccgggttctccggctccggctccggcaccgactacaccctgaccatctcctcctgcagcccaggacttcgccactactac  
 30 tgcattggccagaccatctcctctacaccttcggccagggcaccaagctggagatcaag (SEQ ID NO:76)

IgG4 hinge nucleic acid sequence (36nt)

GAGAGCAAGTACGGACCGCCCTGCCCCCCTTGCCCT (SEQ ID NO:77)

IgG4 hinge amino acid sequence:

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**ESKYGPPCPPCP (SEQ ID NO:78)**

CD28 TM nucleic acid sequence (84nt)

ATGTTCTGGGTGCTGGTGGTGGTCGGAGGCGTGCTGGCCTGCTACAGCCTGCTGG  
5 TCACCGTGGCCTTCATCATCTTTGGGTG (SEQ ID NO:79)

CD28 TM amino acid sequence:

**MFWVLVVVGGVLACYSLLVTVAFIIFWV (SEQ ID NO:80)**

4-1BB nucleic acid sequence

AAACGGGGCAGAAAGAACTCCTGTATATATTCAAACAACCATTTATGAGACCA  
GTACAAACTACTCAAGAGGAAGATGGCTGTAGCTGCCGATTTCCAGAAGAAGAA  
GAAGGAGGATGTGAACTG (SEQ ID NO:81)

15 CD3z nucleic acid sequence

CGGGTGAAGTTCAGCAGAAGCGCCGACGCCCTGCCTACCAGCAGGGCCAGAAT  
CAGCTGTACAACGAGCTGAACCTGGGCAGAAGGGAAGAGTACGACGTCCTGGAT  
AAGCGGAGAGGCCGGGACCCTGAGATGGGCGGCAAGCCTCGGCCGAAGAACCC  
CCAGGAAGGCCTGTATAACGAACTGCAGAAAGACAAGATGGCCGAGGCCTACA  
20 GCGAGATCGGCATGAAGGGCGAGCGGAGGCGGGGCAAGGGCCACGACGGCCTG  
TATCAGGGCCTGTCCACCGCCACCAAGGATACCTACGACGCCCTGCACATGCAG  
GCCCTGCCCCCAAGG (SEQ ID NO:82)

**TOB1** nucleic acid sequence (2130nt)

25 ATGGCCTTACCAGTGACCGCCTTGCTCCTGCCGCTGGCCTTGCTGCTCCACGCCG  
CCAGGCCGAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCTCCAGG  
GGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAGCTACTTAGC  
CTGGTACCAACAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGATGCATCC  
AACAGGGCCACTGGCATCCCAGCCAGGTTTCAGTGGCAGTGGGTCTGGGACAGAC  
30 TTCACTCTACCATCAGCAGCCTAGAGCCTGAAGATTTTGCAGTTTATTACTGTC  
AGCAGCGTAGCAACTGGCCGATCACCTTCGGCCAAGGGACACGACTGGAGATTA  
AAGGCAGTACTAGCGGTGGTGGCTCCGGGGGCGGTTCCGGTGGGGGCGGCAGCA  
GCGAAGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTCCC  
TGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAATGATTATGCCATGCACTG

5 GGTCCGGCAAGCTCCAGGGAAGGGCCTGGAGTGGGTCTCAACTATTAGTTGGAA  
 TAGTGGTTCCATAGGCTATGCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGA  
 GACAACGCCAAGAAGTCCCTGTATCTGCAAATGAACAGTCTGAGAGCTGAGGAC  
 ACGGCCTTGTATTACTGTGCAAAGATATACAGTACGGCAACTACTACTACGGTA  
 10 TGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCAGGAGGTGGTGGAT  
 CCgaggtgcagctggtggagtccggcgggcgccctggtgcagcccggcggtccctgeggctgtcctgcgcegcctccggettca  
 ccttctccaacttcgacatggcctgggtgcggcaggccccggcaagggcctggtgtgggtgtcctccatcaccaccggcgccgac  
 cagccatctacgccgactccgtgaagggccggtcaccatctcccgggacaacgccaagaacaccctgtacctgcagatgaactcc  
 ctgccccggaggacaccgctgtactactgcgtgcggcagggctactacgacggctaccacctgttcgactactggggccaggg  
 caccctggtgaccgtgtcctccggtggcggtggtcggcggtggtgggtcgggtggcggggatctgacatccagatgaccagt  
 cccctcctccctgtccgctccgtggcgaccgggtgaccatcacctgccggcctcccagggcacatccaactacctgaactggtgta  
 ccagcagaagcccggcaagcccccaagccccctgatctactacacctccaacctgcagtccggcggtccctcccgggttctccggtc  
 cggctccggcaccgactacacctgaccatctcctccctgcagcccaggacttcgccactactactgcattggggccagaccatctcc  
 tctacaccttcggccagggcaccaagetggagatcaagGAGAGCAAGTACGGACCGCCCTGCCCCCT  
 15 TGCCCTATGTTCTGGGTGCTGGTGGTGGTTCGGAGGCGTGCTGGCCTGCTACAGCC  
 TGCTGGTCACCGTGGCCTTCATCATCTTTTGGGTGAAACGGGGCAGAAAGAACT  
 CCTGTATATATTCAAACAACCATTTATGAGACCAGTACAACTACTCAAGAGGA  
 AGATGGCTGTAGCTGCCGATTTCCAGAAGAAGAAGAAGGAGGATGTGAACTGCG  
 GGTGAAGTTCAGCAGAAGCGCCGACGCCCTGCCTACCAGCAGGGCCAGAATCA  
 20 GCTGTACAACGAGCTGAACCTGGGCAGAAGGGAAGAGTACGACGTCCTGGATAA  
 GCGGAGAGGCCGGGACCCTGAGATGGGCGGCAAGCCTCGGCGGAAGAACCCCC  
 AGGAAGGCCTGTATAACGAACTGCAGAAAGACAAGATGGCCGAGGCCTACAGC  
 GAGATCGGCATGAAGGGCGAGCGGAGGCGGGCAAGGGCCACGACGGCCTGTA  
 TCAGGGCCTGTCCACCGCCACCAAGGATACCTACGACGCCCTGCACATGCAGGC  
 25 CCTGCCCCCAAGGTAA (SEQ ID NO:83)

**TOBI** amino acid sequence:

MALPVTALLLPLALLLHAARPEIVLTQSPATLSLSPGERATLSCRASQSVSSYLA  
 WYQQKPGQAPRLLIYDASNRAITGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQ  
 30 QRSNWPITFGQTRLEIKGSTSGGGSGGGSGGGSSSEVQLVESGGGLVQPGRSL  
 RLSCAASGFTFNDYAMHWVRQAPGKGLEWVSTISWNSGSIGYADSVKGRFTISR  
 DNAKKSLLYQMNSLRAEDTALYYCAKDIQYGNYYYGMDVWGQGTITVTVSSGG  
 GGSEVQLVESGGGLVQPGLSLRLSCAASGFTFSNFDMAWVRQAPGKGLVWVSS  
 ITTGADHAIYADSVKGRFTISRDNKNTLYQMNSLRAEDTAVYYCVRHGYD

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GYHLFDYWGQGLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVT  
ITCRASQGISNYLNWYQQKPGKAPKPLIYYTSNLQSGVPSRFSGSGSGTDYTLTIS  
SLQPEDFATYYCMGQTISSYTFGQGTKLEIKESKYGPPCPPCMFWVLVVVGGV  
LACYSLLVTVAFIIFWVKRGRKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEE  
5 GGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGG  
KPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDLGLYQGLSTATKD  
TYDALHMQALPPR (SEQ ID NO:84)

TN-OF-B20-2 (TOB2)

CD8a SP nucleic acid sequence

10 ATGGCCTTACCAGTGACCGCCTTGCTCCTGCCGCTGGCCTTGCTGCTCCACGCCG  
CCAGGCCG (SEQ ID NO:85)

OF V<sub>L</sub> nucleic acid sequence

15 GAAATTGTGTTGACACAGTCTCCAGCCACCTGTCTTTGTCTCCAGGGGAAAGAG  
CCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAGCTACTTAGCCTGGTACCA  
ACAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGATGCATCCAACAGGGC  
CACTGGCATCCCAGCCAGGTTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTC  
ACCATCAGCAGCCTAGAGCCTGAAGATTTTGCAGTTTATTACTGTCAGCAGCGTA  
20 GCAACTGGCCGATCACCTTCGGCCAAGGGACACGACTGGAGATTAAA (SEQ ID  
NO:86)

Linker-1 nucleic acid sequence

25 GGCAGTACTAGCGGTGGTGGCTCCGGGGGCGGTTCCGGTGGGGGCGGCAGCAGC  
(SEQ ID NO:87)

OF V<sub>H</sub> nucleic acid sequence

30 GAAGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTCCCTG  
AGACTCTCCTGTGCAGCCTCTGGATTACCTTTAATGATTATGCCATGCACTGGG  
TCCGGCAAGCTCCAGGGAAGGGCCTGGAGTGGGTCTCAACTATTAGTTGGAATA  
GTGGTTCCATAGGCTATGCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGA  
CAACGCCAAGAAGTCCCTGTATCTGCAAATGAACAGTCTGAGAGCTGAGGACAC  
GGCCTTGTATTACTGTGCAAAAGATATACAGTACGGCAACTACTACTACGGTATG  
GACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA (SEQ ID NO:88)

Linker-2 nucleic acid sequence

GGAGGTGGTGGATCC (SEQ ID NO:89)

B20 V<sub>L</sub> nucleic acid sequence

Gacatccagatgaccagtccccctcctcctgtccgcctcctggtggcgaccgggtgaccatcacctgccgggctcccagggcat  
 ctccaactacctgaactggtaccagcagaagccccggcaaggcccccaagcccctgatctactacacctccaactgcagtcggcgt  
 gccctcccgttctcggctcggctcggcaccgactacacctgaccatctcctcctgcagcccaggacttcgccactactac  
 tgcattggccagaccatctcctctacacctcggccagggcaccaagctggagatcaag (SEQ ID NO:90)

Linker-3 nucleic acid sequence

ggtggcggtggctcggcggtggtgggtggcgggcggtatct (SEQ ID NO:91)

B20 V<sub>H</sub> nucleic acid sequence

Gaggtgcagctggtggagtccggcgggcctggtgcagccggcggtcctgcgggtgtcctgcgccctccggcttcacct  
 ctccaactcgacatggcctgggtgcggcaggccccggcaaggcctggtgtgggtgtcctccatcaccaccggcgccgaccag  
 ccatctacgccgactccgtgaaggccggttaccatctcccgggacaacccaagaacacctgtacctgcagatgaactccctgc  
 gggccgaggacaccgccgtgtactactcgtgcggcacggctactacgacggctaccacctgttcgactactggggccagggcacc  
 ctggtgacctgtctcc (SEQ ID NO:92)

hinge nucleic acid sequence

GAGAGCAAGTACGGACCGCCCTGCCCCCTTGCCCT (SEQ ID NO:93)

CD28 TM nucleic acid sequence

ATGTTCTGGGTGCTGGTGGTGGTCGGAGGCGTGCTGGCCTGCTACAGCCTGCTGG  
 TCACCGTGGCCTTCATCATCTTTGGGTG (SEQ ID NO:94)

4-1BB nucleic acid sequence

AAACGGGGCAGAAAGAACTCCTGTATATATTCAAACAACCATTTATGAGACCA  
 GTACAAACTACTCAAGAGGAAGATGGCTGTAGCTGCCGATTTCCAGAAGAAGAA  
 GAAGGAGGATGTGAACTG (SEQ ID NO:95)

CD3z nucleic acid sequence

CGGGTGAAGTTCAGCAGAAGCGCCGACGCCCTGCCTACCAGCAGGGCCAGAAT

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CAGCTGTACAACGAGCTGAACCTGGGCAGAAGGGAAGAGTACGACGTCCTGGAT  
 AAGCGGAGAGGCCGGGACCCTGAGATGGGCGGCAAGCCTCGGCGGAAGAACCC  
 CCAGGAAGGCCTGTATAACGAACTGCAGAAAGACAAGATGGCCGAGGCCTACA  
 GCGAGATCGGCATGAAGGGCGAGCGGAGGCGGGGCAAGGGCCACGACGGCCTG  
 5 TATCAGGGCCTGTCCACCGCCACCAAGGATACCTACGACGCCCTGCACATGCAG  
 GCCCTGCCCCCAAGG (SEQ ID NO:96)

**TOB2 nucleic acid sequence (2130nt)**

ATGGCCTTACCAGTGACCGCCTTGCTCCTGCCGCTGGCCTTGCTGCTCCACGCCG  
 10 CCAGGCCGGAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCTCCAGG  
 GGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAGCTACTTAGC  
 CTGGTACCAACAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGATGCATCC  
 AACAGGGCCACTGGCATCCCAGCCAGGTTTCAGTGGCAGTGGGTCTGGGACAGAC  
 TTCACTCTCACCATCAGCAGCCTAGAGCCTGAAGATTTTGCAGTTTATTACTGTC  
 15 AGCAGCGTAGCAACTGGCCGATCACCTTCGGCCAAGGGACACGACTGGAGATTA  
 AAGGCAGTACTAGCGGTGGTGGCTCCGGGGGCGGTTCCGGTGGGGGCGGCAGCA  
 GCGAAGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTCCC  
 TGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAATGATTATGCCATGCACTG  
 GGTCCGGCAAGCTCCAGGGAAGGGCCTGGAGTGGGTCTCAACTATTAGTTGGAA  
 20 TAGTGGTTCATAGGCTATGCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGA  
 GACAACGCCAAGAAGTCCCTGTATCTGCAAATGAACAGTCTGAGAGCTGAGGAC  
 ACGGCCTTGTATTACTGTGCAAAGATATACAGTACGGCAACTACTACTACGGTA  
 TGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCAGGAGGTGGTGGAT  
 CCGacatccagatgaccagtccccctcctcctgtccgcctccgtgggcgaccgggtgaccatcacctgccgggctcccaggg  
 25 catctccaactacctgaactgtaccagcagaagccccggcaaggcccccaagcccctgatctactacacctccaacctgcagtccgg  
 cgtgccctcccgggttctccggctccggctccggcaccgactacacctgaccatctcctcctgcagcccaggacttgcacactac  
 tactgcatgggccagaccatctcctctacacctcggccaggcaccaggctggagatcaagggtggcggtggctcgggcgggtgg  
 tgggtcgggtggcgccgatctgaggtgcagctgggtggagtccggcgggcctgggtgcagcccggcggtcctcctgcggctgtcc  
 tgcgccctccggcttacctctccaactcgcacatggcctgggtgcggcaggccccggcaagggcctgggtgtgggtgtcctcc  
 30 atcaccaccggcgccgaccacgccatctacgccgactccgtgaaggcgccggtcaccatctcccgggacaacccaagaacacct  
 gtacctgcagatgaactccctcggggccaggacaccgccgtgtactactgcgtgcggcagggctactacgacggctaccacctgtt  
 cgactactggggccagggcacctgggtgacctgtcctccGAGAGCAAGTACGGACCGCCCTGCCCCC  
 TTGCCCTATGTTCTGGGTGCTGGTGGTGGTCGGAGGCGTGCTGGCCTGCTACAGC  
 CTGCTGGTCACCGTGGCCTTCATCATCTTTTGGGTGAAACGGGGCAGAAAGAAAC

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TCCTGTATATATTCAAACAACCATTTATGAGACCAGTACAAACTACTCAAGAGGA  
AGATGGCTGTAGCTGCCGATTTCCAGAAGAAGAAGAAGGAGGATGTGAACTGCG  
GGTGAAGTTCAGCAGAAGCGCCGACGCCCTGCCTACCAGCAGGGCCAGAATCA  
GCTGTACAACGAGCTGAACCTGGGCAGAAGGGAAGAGTACGACGTCCTGGATAA  
GCGGAGAGGCCGGGACCCTGAGATGGGCGGCAAGCCTCGGCGGAAGAACCCCC  
AGGAAGGCCTGTATAACGAACTGCAGAAAGACAAGATGGCCGAGGCCTACAGC  
GAGATCGGCATGAAGGGCGAGCGGAGGCGGGGCAAGGGCCACGACGGCCTGTA  
TCAGGGCCTGTCCACCGCCACCAAGGATACCTACGACGCCCTGCACATGCAGGC  
CCTGCCCCCAAGGTAA (SEQ ID NO:97)

TOB2 amino acid sequence:

MALPVTALLLPLALLLHAARPEIVLTQSPATLSLSPGERATLSCRASQSVSSYLA  
WYQQKPGQAPRLLIYDASNRAITGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQ  
QRSNWPITFGQGTRLEIKGSTSGGGSGGGSGGGGSSEVQLVESGGGLVQPGRSL  
RLSCAASGFTFNDYAMHWVRQAPGKGLEWVSTISWNSGSIYADSVKGRFTISR  
DNAKKSLLYQMNSLRAEDTALYYCAKDIQYGNYYYGMDVWGQGTITVTVSSGG  
GGSDIQMTQSPSSLSASVGDRVTITCRASQGISNYLNWYQQKPKAPKPLIYYTS  
NLQSGVPSRFSGSGSGTDYTLTISSLQPEDFATYYCMGQTISSYTFGQGTKLEIK  
GGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFSNFDMAWV  
RQAPGKGLVWVSSITGADHAIYADSVKGRFTISRDNKNTLYQMNSLRAEDT  
AVYYCVRHGYDGYHFLFDYWQGTLVTVSSESKYGPCCPPCFMWVWLVVVG  
VLACYSLLVTVAFIIFWVKRGRKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEE  
EGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDRRGRDP  
EMG  
GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGGHDGLYQGLSTATK  
DTYDALHMQUALPPR (SEQ ID NO:98)

TN-OF-B20-3 (TOB3)

CD8a SP nucleic acid sequence

ATGGCCTTACCAGTGACCGCCTTGCTCCTGCCGCTGGCCTTGCTGCTCCACGCCG  
CCAGGCCG (SEQ ID NO:99)

OF V<sub>H</sub> nucleic acid sequence

GAAGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTCCCTG  
AGACTCTCCTGTGCAGCCTCTGGATTACCTTTAATGATTATGCCATGCACTGGG

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5 TCCGGCAAGCTCCAGGGAAGGGCCTGGAGTGGGTCTCAACTATTAGTTGGAATA  
GTGGTTCCATAGGCTATGCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGA  
CAACGCCAAGAAGTCCCTGTATCTGCAAATGAACAGTCTGAGAGCTGAGGACAC  
GGCCTTGTATTACTGTGCAAAGATATACAGTACGGCAACTACTACTACGGTATG  
GACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA (SEQ ID NO:100)

Linker-1 nucleic acid sequence

10 GGCAGTACTAGCGGTGGTGGCTCCGGGGGCGGTTCCGGTGGGGGCGGCAGCAGC  
(SEQ ID NO:101)

OF V<sub>L</sub> nucleic acid sequence

15 GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCTCCAGGGGAAAGAG  
CCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAGCTACTTAGCCTGGTACCA  
ACAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGATGCATCCAACAGGGC  
CACTGGCATCCCAGCCAGGTTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTC  
ACCATCAGCAGCCTAGAGCCTGAAGATTTTGCAGTTTATTACTGTCAGCAGCGTA  
GCAACTGGCCGATCACCTTCGGCCAAGGGACACGACTGGAGATTAAA (SEQ ID  
NO:102)

20 Linker-2 nucleic acid sequence

GGAGGTGGTGGATCC (SEQ ID NO:103)

B20 V<sub>L</sub> nucleic acid sequence

25 Gacatccagatgaccagtgccccctcctccctgtcgcctccgtgggagaccgggtgaccatcacctgccgggctcccaggcat  
ctccaactacctgaactggtaccagcagaagcccggcaaggcccccaagcccctgatctactacacctccaacctgcagtcggcgt  
gccctcccggttctccggctccggctccggcaccgactacaccctgaccatctcctcctgcagcccaggacttcgccactactac  
tgcattggccagaccatctcctctacaccttcggccagggcaccagctggagatcaag (SEQ ID NO:104)

Linker-3 nucleic acid sequence

30 ggtggcggtggctcgggcggtggtgggtcgggtggcggggatct (SEQ ID NO:105)

B20 V<sub>H</sub> nucleic acid sequence

Gaggtgcagctggtggagtccggcgggcgccctggtgcagcccggcggtccctgcggctgtcctgcgccctccggcttcacctt  
ctccaacttcgacatggcctgggtgcggcaggccccggcaaggcgctggtgtgggtgtcctccatcaccaccggcgccgaccag

ccatctacgccgactccgtgaagggccggttcaccatctcccgggacaacgccaagaacaccctgtacctgcagatgaactccctgc  
gggccgaggacaccgcccgtgtactactgcgtgcggcacggctactacgacggctaccacctgttcgactactggggccagggcacc  
ctggtgaccgtgtcctcc (SEQ ID NO:106)

5 hinge nucleic acid sequence

GAGAGCAAGTACGGACCGCCCTGCCCCCTTGCCCT (SEQ ID NO:107)

CD28 TM nucleic acid sequence

10 ATGTTCTGGGTGCTGGTGGTGGTCGGAGGCGTGCTGGCCTGCTACAGCCTGCTGG  
TCACCGTGGCCTTCATCATCTTTGGGTG (SEQ ID NO:108)

4-1BB nucleic acid sequence

15 AAACGGGGCAGAAAGAACTCCTGTATATATTCAAACAACCATTTATGAGACCA  
GTACAAACTACTCAAGAGGAAGATGGCTGTAGCTGCCGATTTCCAGAAGAAGAA  
GAAGGAGGATGTGAACTG (SEQ ID NO:109)

CD3z nucleic acid sequence

20 CGGGTGAAGTTCAGCAGAAGCGCCGACGCCCTGCCTACCAGCAGGGCCAGAAT  
CAGCTGTACAACGAGCTGAACCTGGGCAGAAGGGAAGAGTACGACGTCCTGGAT  
AAGCGGAGAGGCCGGGACCCTGAGATGGGCGGCAAGCCTCGGCCGGAAGAACCC  
CCAGGAAGGCCTGTATAACGAACTGCAGAAAGACAAGATGGCCGAGGCCTACA  
GCGAGATCGGCATGAAGGGCGAGCGGAGGCGGGGCAAGGGCCACGACGGCCTG  
TATCAGGGCCTGTCCACCGCCACCAAGGATACCTACGACGCCCTGCACATGCAG  
GCCCTGCCCCCAAGG (SEQ ID NO:110)

25 **TOB3** nucleic acid sequence (2130nt)

30 ATGGCCTTACCAGTGACCGCCTTGCTCCTGCCGCTGGCCTTGCTGCTCCACGCCG  
CCAGGCCGGAAGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGCA  
GGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTTAATGATTATGCCATG  
CACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTGGAGTGGGTCTCAACTATTAGT  
TGGAATAGTGGTTCCATAGGCTATGCGGACTCTGTGAAGGGCCGATTCACCATCT  
CCAGAGACAACGCCAAGAAGTCCCTGTATCTGCAAATGAACAGTCTGAGAGCTG  
AGGACACGGCCTTGTATTACTGTGCAAAAGATATACAGTACGGCAACTACTACT  
ACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCAGGCAGTA

CTAGCGGTGGTGGCTCCGGGGGCGGTTCCGGTGGGGGCGGCAGCAGCGAAATTG  
 TGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACCCT  
 CTCCTGCAGGGCCAGTCAGAGTGTTAGCAGCTACTTAGCCTGGTACCAACAGAA  
 ACCTGGCCAGGCTCCCAGGCTCCTCATCTATGATGCATCCAACAGGGCCACTGGC  
 5 ATCCCAGCCAGGTTCACTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCA  
 GCAGCCTAGAGCCTGAAGATTTTGCAGTTTATTACTGTCAGCAGCGTAGCAACTG  
 GCCGATCACCTTCGGCCAAGGGACACGACTGGAGATTAAGGAGGTGGTGGATC  
 CGacatccagatgaccagtgccccctcctcctgtccgcctcctggggcgaccgggtgaccatcacctgccggcctcccagggc  
 atctccaactacatgaactgggtaccagcagaagcccggcaaggcccccaagcccctgatctactacacctccaacctgcagtccggc  
 10 gtgccctcccgggttctccggctccggctccggcaccgactacacctgaccatctcctcctgcagcccaggacttccaccactact  
 actgcatgggcccagaccatctcctctacaccttcggccagggcaccaagctggagatcaagggtggcgggtggctcgggcccgggtgt  
 gggtcgggtggcgccgatctgaggtgcagctgggtggagtccggcggcgccctgggtgcagcccggcggtcctcctgcggctgtcct  
 gcgccgcctcccggcttaccttctccaacttcgacatggcctgggtgcggcaggccccggcaaggcctgggtgtgggtgtcctcca  
 tcaccaccggcgccgaccacgccatctacgccgactccgtgaaggggccgggtcaccatctcccgggacaacccaagaacacct  
 15 gtacctgcagatgaactccctgcgggcccaggacaccgccgtgtactactgcgtgcggcagcggtactacgacggctaccacctgtt  
 cgactactggggccagggcacctgggtgacctgtctcccGAGAGCAAGTACGGACCGCCCTGCCCCC  
 TTGCCCTATGTTCTGGGTGCTGGTGGTGGTTCGGAGGCGTGCTGGCCTGCTACAGC  
 CTGCTGGTCACCGTGGCCTTCATCATCTTTTGGGTGAAACGGGGCAGAAAGAAAC  
 TCCTGTATATATTCAAACAACCATTTATGAGACCAGTACAAACTACTCAAGAGGA  
 20 AGATGGCTGTAGCTGCCGATTTCCAGAAGAAGAAGAAGGAGGATGTGAACTGCG  
 GGTGAAGTTCAGCAGAAGCGCCGACGCCCTGCCTACCAGCAGGGCCAGAATCA  
 GCTGTACAACGAGCTGAACCTGGGCAGAAGGGAAGAGTACGACGTCCTGGATAA  
 GCGGAGAGGCCGGGACCCTGAGATGGGCGGCAAGCCTCGGCGGAAGAACCCCC  
 AGGAAGGCCTGTATAACGAAGTGCAGAAAGACAAGATGGCCGAGGCCTACAGC  
 25 GAGATCGGCATGAAGGGCGAGCGGAGGCGGGCAAGGGCCACGACGGCCTGTA  
 TCAGGGCCTGTCCACCGCCACCAAGGATACCTACGACGCCCTGCACATGCAGGC  
 CCTGCCCCCAAGGTAA (SEQ ID NO:111)

**TOB3** amino acid sequence:

30 MALPVTALLLPLALLLHAARPEVQLVESGGGLVQPGRSLRLSCAASGFTFNDYA  
 MHWVRQAPGKGLEWVSTISWNSGSIGYADSVKGRFTISRDNAKKSLYLQMNSL  
 RAEDTALYYCAKDIQYGNYYYGMDVWGQGTTVTVSSGSTSGGGSGGGSGGGG  
 SSEIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNR  
 ATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPITFGQGRLEIKGG

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GGSDIQMTQSPSSLSASVGDRTITCRASQGISNYLNWYQQKPGKAPKPLIYYTS  
NLQSGVPSRFSGSGSGTDYTLTISSLQPEDFATYYCMGQTISSYTFGQGTKLEIK  
GGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFSNFDMAWV  
RQAPGKGLVWVSSITGADHAIYADSVKGRFTISRDNKNTLYLQMNSLRAEDT  
AVYYCVRHGYYDGYHLFDYWGGTLVTVSSESKYGPPCPPCPMFVWLVVVGG  
VLACYSLLVTVAFIIFWVKRGRKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEE  
EGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPENMG  
GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGGHDGLYQGLSTATK  
DTYDALHMQUALPPR (SEQ ID NO:112)

TN-OF-B20-4 (TOB4)

CD8a SP nucleic acid sequence

ATGGCCTTACCAGTGACCGCCTTGCTCCTGCCGCTGGCCTTGCTGCTCCACGCCG  
CCAGGCCG (SEQ ID NO:113)

OF V<sub>H</sub> nucleic acid sequence

GAAGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTCCCTG  
AGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAATGATTATGCCATGCACTGGG  
TCCGGCAAGCTCCAGGGAAGGGCCTGGAGTGGGTCTCAACTATTAGTTGGAATA  
GTGGTTCCATAGGCTATGCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGA  
CAACGCCAAGAAGTCCCTGTATCTGCAAATGAACAGTCTGAGAGCTGAGGACAC  
GGCCTTGTATTACTGTGCAAAGATATACAGTACGGCAACTACTACTACGGTATG  
GACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA (SEQ ID NO:114)

Linker-1 nucleic acid sequence

GGCAGTACTAGCGGTGGTGGCTCCGGGGGCGGTTCCGGTGGGGGCGGCAGCAGC  
(SEQ ID NO:115)

OF V<sub>L</sub> nucleic acid sequence

GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCTCCAGGGGAAAGAG  
CCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAGCTACTTAGCCTGGTACCA  
ACAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGATGCATCCAACAGGGC  
CACTGGCATCCCAGCCAGGTTCCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTC  
ACCATCAGCAGCCTAGAGCCTGAAGATTTTGCAGTTTATTACTGTCAGCAGCGTA

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GCAACTGGCCGATCACCTTCGGCCAAGGGACACGACTGGAGATTA (SEQ ID NO:116)

Linker-2 nucleic acid sequence

5 GGAGGTGGTGGATCC (SEQ ID NO:117)

B20 V<sub>H</sub> nucleic acid sequence

10 Gaggtgcagctggtggagtccggcggcggcctggtgcagcccggcggctcctgaggctgctctgcccgcctccggcttcacctt  
ctccaacttcgacatggcctgggtgcccaggccccggcaagggcctggtgtgggtgctctccatcaccaccggcggcaccacg  
ccatctacgccgactccgtgaaggccgggtaccatctcccgggacaacccaagaacaccctgtacctgcagatgaactccctgc  
gggccgaggacaccgccgtgtactactgctgcccacggctactacacggctaccacctgtcactactggggccaggccacc  
ctggtgaccgtgtctcc (SEQ ID NO:118)

Linker-3 nucleic acid sequence

15 ggtggcgggtggctcggcgggtgggtgggtggcggcgatct (SEQ ID NO:119)

B20 V<sub>L</sub> nucleic acid sequence

20 Gacatccagatgaccagtcctcctctcctgctccgctcctggtggcgaccgggtgaccatcacctgccgggcctcccaggcat  
ctccaactacctgaactggtaccagcagaagcccggcaagggcccccaagcccctgatctactacacctccaacctgcagtcggcgt  
gccctcccgttctccgctcggctcggcaccgactacacctgaccatctcctcctgcagcccaggacttegccacctactac  
tgcattggccagaccatctcctctacaccttcggccaggccaccaagctggagatcaag (SEQ ID NO:120)

hinge nucleic acid sequence

25 GAGAGCAAGTACGGACCGCCCTGCCCCCTTGCCCT (SEQ ID NO:121)

CD28 TM nucleic acid sequence

ATGTTCTGGGTGCTGGTGGTGGTCGGAGGCGTGCTGGCCTGCTACAGCCTGCTGG  
TCACCGTGGCCTTCATCATCTTTGGGTG (SEQ ID NO:122)

4-1BB nucleic acid sequence

30 AAACGGGGCAGAAAGAACTCCTGTATATATTCAAACAACCATTTATGAGACCA  
GTACAAACTACTCAAGAGGAAGATGGCTGTAGCTGCCGATTTCCAGAAGAAGAA  
GAAGGAGGATGTGAACTG (SEQ ID NO:123)

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CD3z nucleic acid sequence

CGGGTGAAGTTCAGCAGAAGCGCCGACGCCCTGCCTACCAGCAGGGCCAGAAT  
 CAGCTGTACAACGAGCTGAACCTGGGCAGAAGGGAAGAGTACGACGTCCTGGAT  
 AAGCGGAGAGGCCGGGACCCTGAGATGGGCGGCAAGCCTCGGGCGGAAGAACCC  
 5 CCAGGAAGGCCTGTATAACGAACTGCAGAAAGACAAGATGGCCGAGGCCTACA  
 GCGAGATCGGCATGAAGGGCGAGCGGAGGGCGGGGCAAGGGCCACGACGGCCTG  
 TATCAGGGCCTGTCCACCGCCACCAAGGATACCTACGACGCCCTGCACATGCAG  
 GCCCTGCCCCCAAGG (SEQ ID NO:124)

**TOB4** nucleic acid sequence (2130nt)

ATGGCCTTACCAGTGACCGCCTTGCTCCTGCCGCTGGCCTTGCTGCTCCACGCCG  
 CCAGGCCGGAAGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGCA  
 GGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTTAATGATTATGCCATG  
 CACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTGGAGTGGGTCTCAACTATTAGT  
 15 TGGAATAGTGGTTCCATAGGCTATGCGGACTCTGTGAAGGGCCGATTACCATCT  
 CCAGAGACAACGCCAAGAAGTCCCTGTATCTGCAAATGAACAGTCTGAGAGCTG  
 AGGACACGGCCTTGTATTACTGTGCAAAAGATATACAGTACGGCAACTACTACT  
 ACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCAGGCAGTA  
 CTAGCGGTGGTGGCTCCGGGGGCGGTTCCGGTGGGGGCGGCAGCAGCGAAATTG  
 20 TGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACCCT  
 CTCCTGCAGGGCCAGTCAGAGTGTTAGCAGCTACTTAGCCTGGTACCAACAGAA  
 ACCTGGCCAGGCTCCCAGGCTCCTCATCTATGATGCATCCAACAGGGCCACTGGC  
 ATCCCAGCCAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCA  
 GCAGCCTAGAGCCTGAAGATTTTGCAGTTTATTACTGTCAGCAGCGTAGCAACTG  
 25 GCCGATCACCTTCGGCCAAGGGACACGACTGGAGATTAAGGAGGTGGTGGATC  
 Cgaggtgcagctggtggagtccggcgggcctggtgcagcccggcggtccctgcggtgtcctgcgcccctccggcttcacc  
 ttctcaacttcgacatggcctgggtgcggcaggccccggcaagggcctggtgtgggtgtcctccatcaccaccggcgccgacca  
 cgccatctacgccgactccgtgaaggccggttcaccatctcccgggacaacgccaagaacaccctgtacctgcagatgaactccct  
 gggggccgaggacaccgcccgtgtactactgcgtgcggcacggctactacgacggctaccacctgttcgactactggggccagggc  
 30 accctggtgaccgtgtcctccggtggcggtggctcggcggtggtgggtcgggtggcgccgatctGacatccagatgaccagtc  
 cccctcctcctgtcgcctccgtgggcgaccgggtgaccatcacctgccgggctcccagggcatctccaactacctgaactggtac  
 cagcagaagcccggcaagggcccccaagcccctgatctactacacctccaacctgcagtccggcgtgcctcccgttctccggctcc  
 ggctccggcaccgactacacctgaccatctcctcctgcagcccgaggacttcgccactactactgcatgggcccagaccatctct  
 cctacaccttcggccagggcaccagctggagatcaagGAGAGCAAGTACGGACCGCCCTGCCCCCT

5 TGCCCTATGTTCTGGGTGCTGGTGGTGGTTCGGAGGCGTGCTGGCCTGCTACAGCC  
 TGCTGGTCACCGTGGCCTTCATCATCTTTTGGGTGAAACGGGGCAGAAAGAACT  
 CCTGTATATATTCAAACAACCATTTATGAGACCAGTACAACTACTCAAGAGGA  
 AGATGGCTGTAGCTGCCGATTTCCAGAAGAAGAAGAAGGAGGATGTGAACTGCG  
 10 GGTGAAGTTCAGCAGAAGCGCCGACGCCCTGCCTACCAGCAGGGCCAGAATCA  
 GCTGTACAACGAGCTGAACCTGGGCAGAAGGGAAGAGTACGACGTCCTGGATAA  
 GCGGAGAGGCCGGGACCCTGAGATGGGCGGCAAGCCTCGGCGGAAGAACCCCC  
 AGGAAGGCCTGTATAACGAACTGCAGAAAGACAAGATGGCCGAGGCCTACAGC  
 GAGATCGGCATGAAGGGCGAGCGGAGGCGGGGCAAGGGCCACGACGGCCTGTA  
 15 TCAGGGCCTGTCCACCGCCACCAAGGATACCTACGACGCCCTGCACATGCAGGC  
 CCTGCCCCCAAGGTAA (SEQ ID NO:125)

***TOB4*** amino acid sequence:

15 MALPVTALLLPLALLHAARPEVQLVESGGGLVQPGRSLRLSCAASGFTFNDYA  
 MHWVRQAPGKGLEWVSTISWNSGSIGYADSVKGRFTISRDNAKKSLYLQMNSL  
 RAEDTALYYCAKDIQYGNYYYGMDVWGQGTITVTVSSGSTSGGGSGGGSGGGG  
 SSEIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNR  
 ATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPITFGQGRLEIKGG  
 20 GGSEVQLVESGGGLVQPGGSLRLSCAASGFTFSNFDMAWVRQAPGKGLVWVSS  
 ITTGADHAIYADSVKGRFTISRDNAKNTLYLQMNSLRAEDTAVYYCVRHGYD  
 GYHLFDYWGQGLTVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVDRVT  
 ITCRASQGISNYLNWYQQKPKAPKPLIYYTSNLQSGVPSRFSGSGSGTDYTLTIS  
 SLQPEDFATYYCMGQTISSYTFGQGTKLEIKESKYGPPCPPCFMFWLVVVGGV  
 LACYSLLVTVAFIIFWVKRGRKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEE  
 25 GGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDRRGRDPEMGG  
 KPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHGGLYQGLSTATKD  
 TYDALHMQALPPR (SEQ ID NO:126)

30 OF-V<sub>H</sub>-CDR1: NDYAMH (SEQ ID NO: 127)

OF-V<sub>H</sub>-CDR2: TISWNSGSIGYADSVKG (SEQ ID NO: 128)

OF-V<sub>H</sub>-CDR3: DIQYGNYYYGMDV (SEQ ID NO: 129)

OF-V<sub>L</sub>-CDR1: RASQSVSSYLA (SEQ ID NO: 130)

OF-V<sub>L</sub>-CDR2: DASNRAT (SEQ ID NO: 131)

5 OF-V<sub>L</sub>-CDR3: QQRSNWPIT (SEQ ID NO: 132)

**BCMA-20 V<sub>L</sub>**

Region	Sequence Fragment	Residues of SEQ ID No:12	Length	SEQ ID No:
LFR1	DIQMTQSPSSLSASVGDRVITIC	1 - 23	23	SEQ ID No:133
CDR-L1	RASQGISNYLN	24 - 34	11	SEQ ID No:134
LFR2	WYQQKPGKAPKPLIY	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-20 V<sub>H</sub>**

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	SITGADHAIYADSVKG	50 - 66	17	SEQ ID No:143
HFR3	RFTISRDNKNTLYLQMNSLRAEDTAVYYCVR	67 - 98	32	SEQ ID No:144
CDR-H3	HGYDGYHFLFDY	99 - 110	12	SEQ ID No:145
HFR4	WGQGTLVTVSS	111 - 121	11	SEQ ID No:146

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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.

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## CLAIMS

1. 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.
2. The bispecific CAR of claim 1, wherein  $V_{L1}$  is located at the N-terminus of  $V_{H1}$ , or wherein  $V_{H1}$  is located at the N-terminus of  $V_{L1}$ ; optionally wherein  $V_{L2}$  is located at the N-terminus of  $V_{H2}$ , or wherein  $V_{H2}$  is located at the N-terminus of  $V_{L2}$ .
3. The bispecific CAR of claim 1 or claim 2, wherein  $V_{L1}$  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; optionally wherein  $V_{L2}$  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.
4. The bispecific CAR of any one of claims 1 to 3, 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.

5. The bispecific CAR of any one of claims 1 to 4, 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,

optionally 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;

optionally wherein the cytoplasmic signaling domain comprises a cytoplasmic signaling domain of CD3 $\zeta$ ;

optionally wherein the hinge region comprises a hinge region of IgG4, CD8, CD28, CD137, or combinations thereof;

optionally wherein the transmembrane domain comprises a transmembrane domain of CD8, CD28, CD3 $\epsilon$ , CD45, CD4, CD5, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137, CD154, or combinations thereof.

6. The bispecific CAR of any one of claims 1 to 5, 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.

7. An immune cell expressing the bispecific CAR of any one of claims 1 to 6, optionally wherein the immune cell is a T cell or a natural killer (NK) cell.

8. A nucleic acid encoding the bispecific CAR of any one of claims 1 to 6.

9. A vector comprising the nucleic acid of claim 8.

10. A pharmaceutical composition, comprising the bispecific CAR of any one of claims 1 to 6, the immune cell of claim 7, the nucleic acid of claim 8, or the vector of claim 9.

11. A method of treating an autoimmune disorder in a subject, the method comprising administering the immune cell of claim 7, or the pharmaceutical composition of claim 10, to the subject.
12. The method of claim 11, wherein the autoimmune disorder is systemic lupus erythematosus (SLE), systemic sclerosis, inflammatory myopathy, systemic scleroderma, multiple sclerosis, myasthenia gravis, a myositis autoantibody-driven disease, or neuromyelitis optica.
13. The method of claim 12, wherein the inflammatory myopathy is polymyositis, dermatomyositis, or inclusion-body myositis.
14. The method of claim 12, wherein the subject with SLE has lupus nephritis.
15. A method of treating a cancer, the method comprising administering the immune cell of claim 7, or the pharmaceutical composition of claim 10, to a subject in need thereof.
16. The method of claim 15, wherein the cancer is a hematologic cancer.
17. The method of claim 15, wherein the cancer is a B-cell malignancy.
18. The method of claim 15, wherein the cancer is Hodgkin's lymphoma, non-Hodgkin's lymphoma, leukemia, and/or multiple myeloma.
19. The method of claim 15, wherein the cancer is 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.
20. The method of any one of claims 11 to 19, wherein the immune cell is allogeneic or autologous.

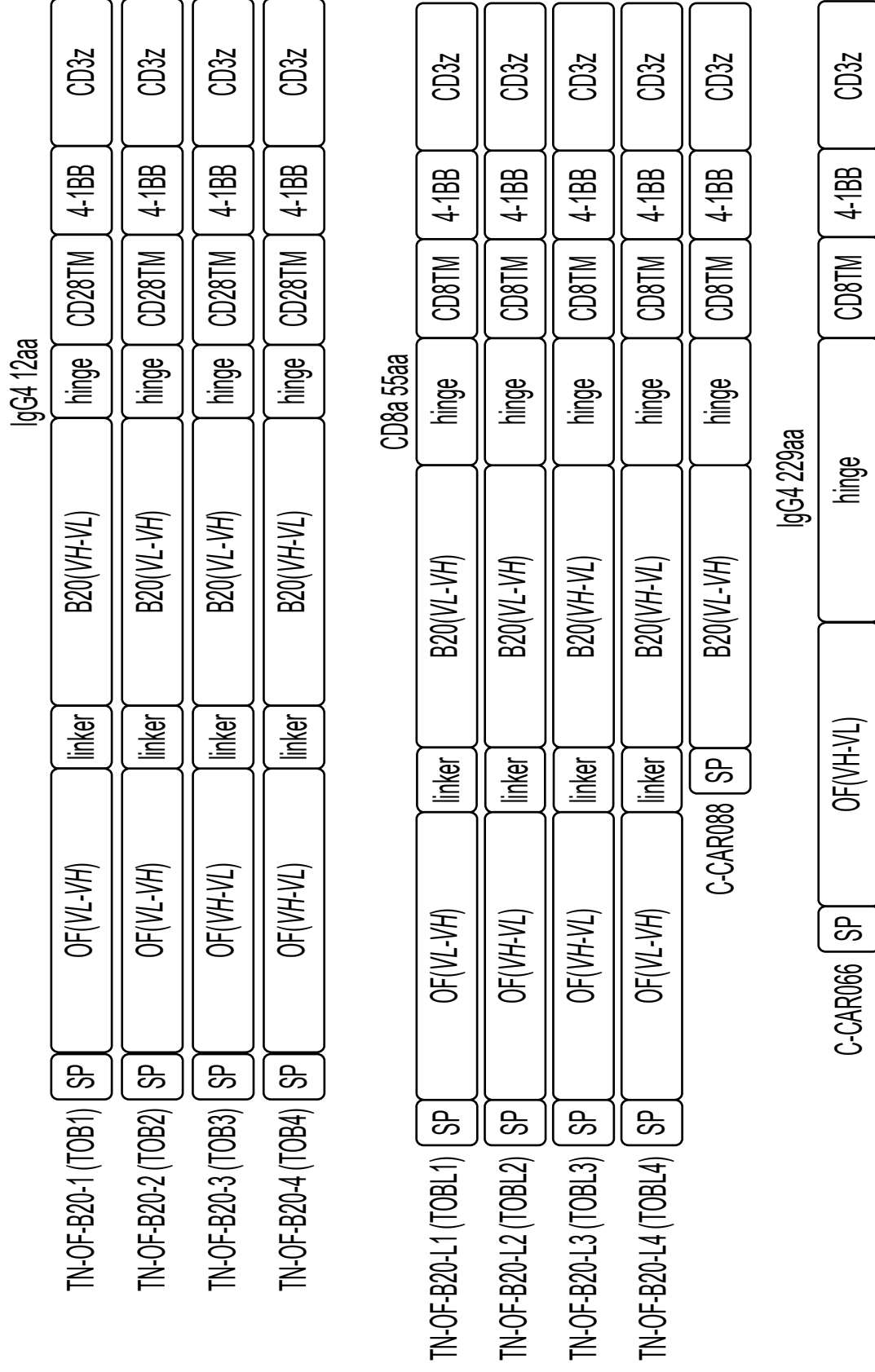


FIG. 1

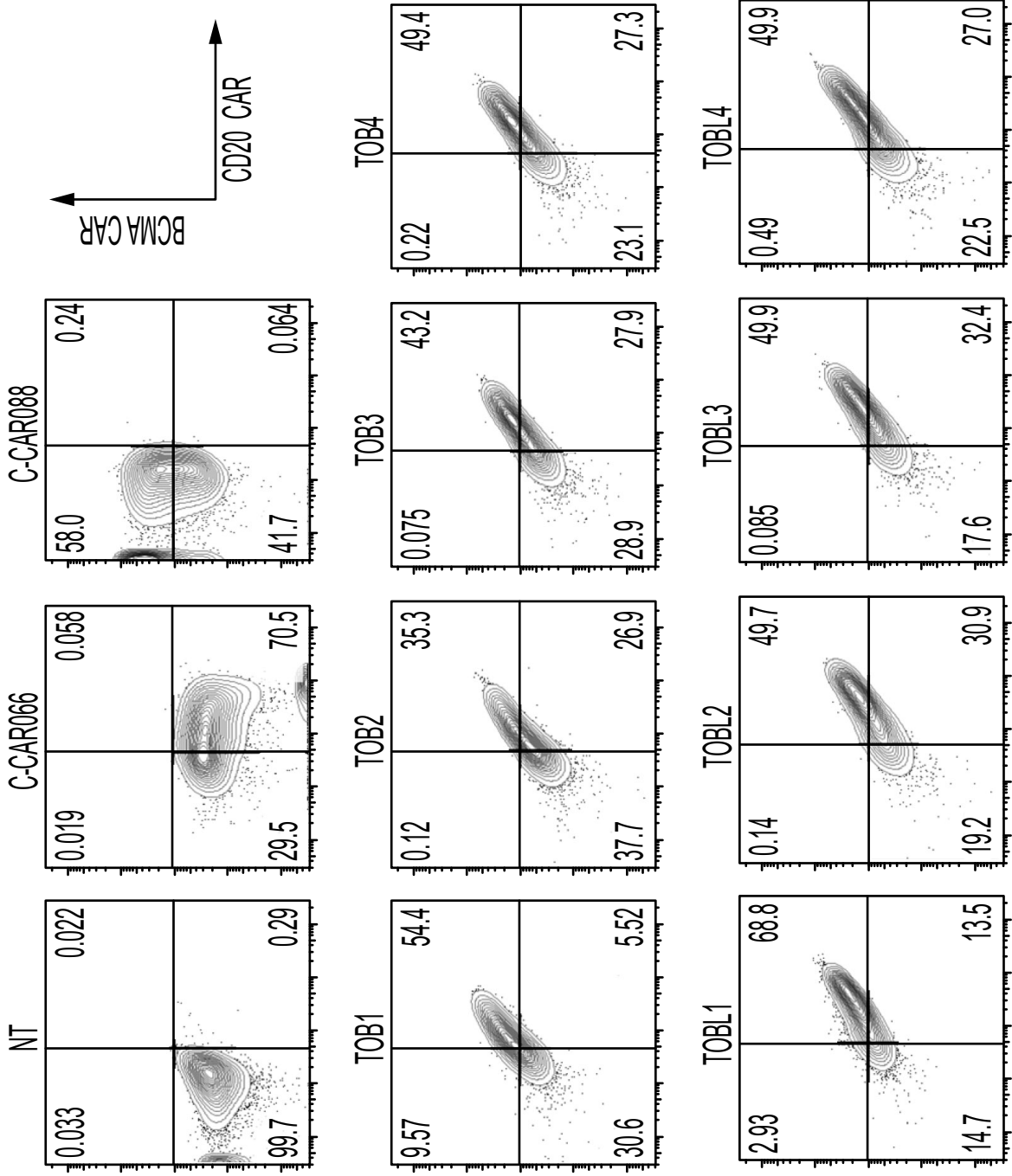


FIG. 2

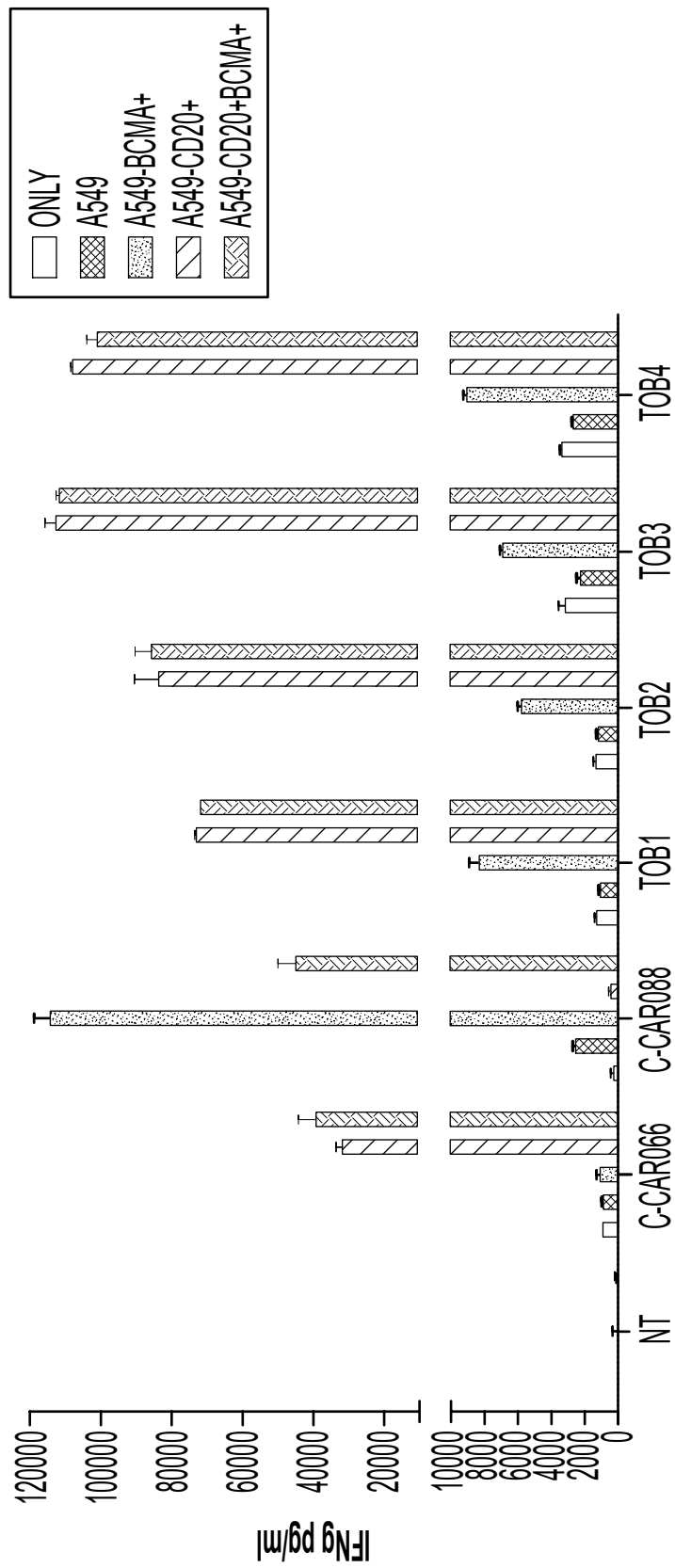


FIG. 3A

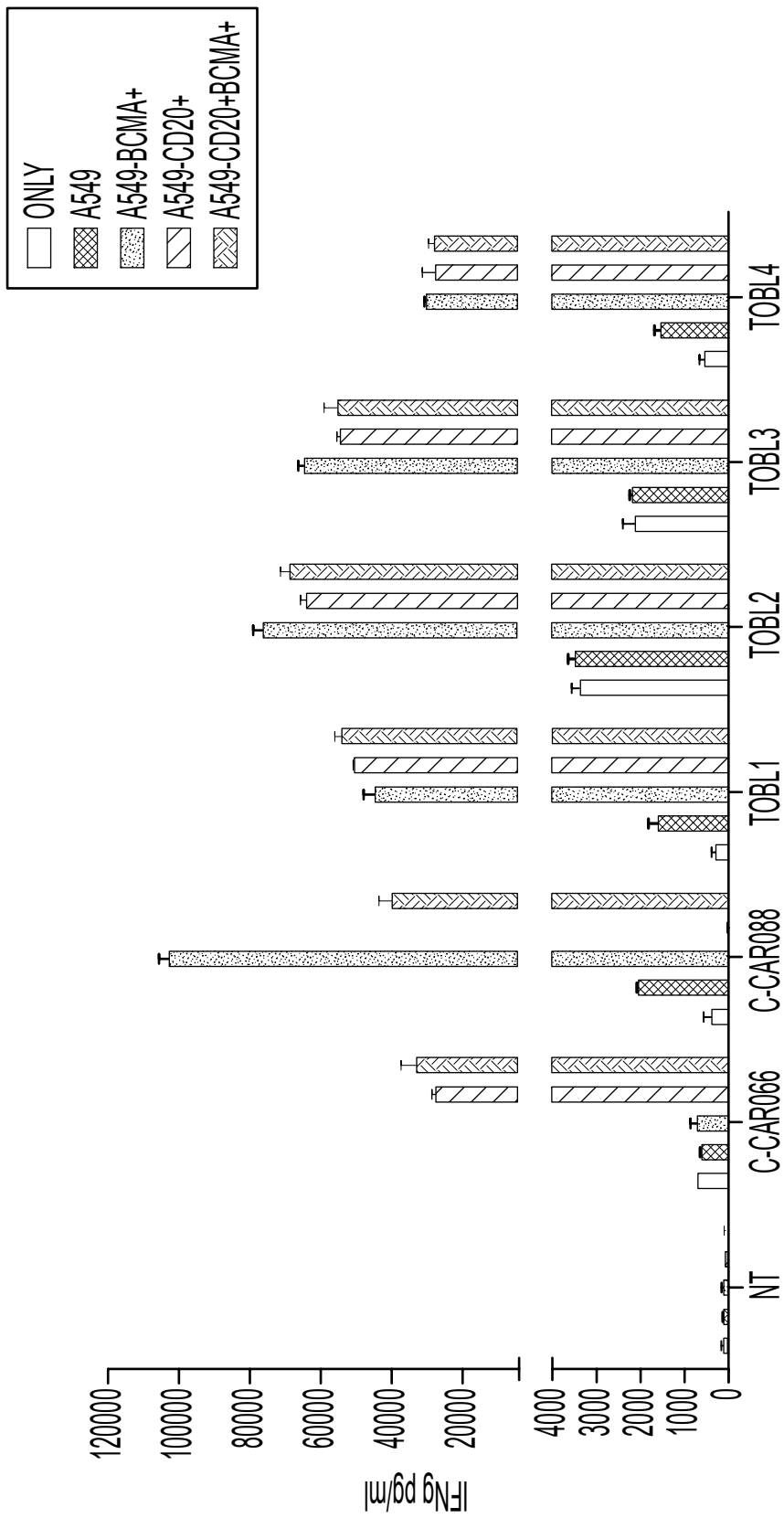


FIG. 3B

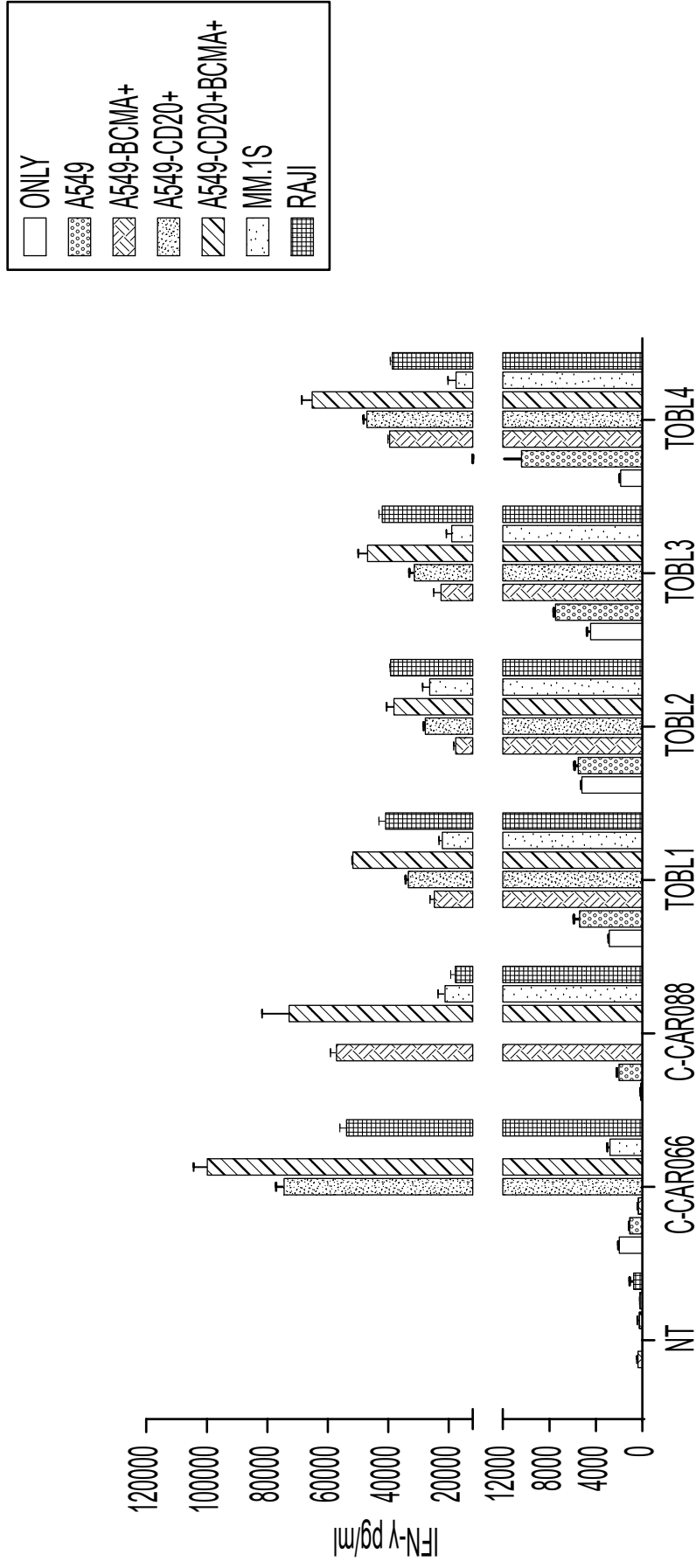


FIG. 3C

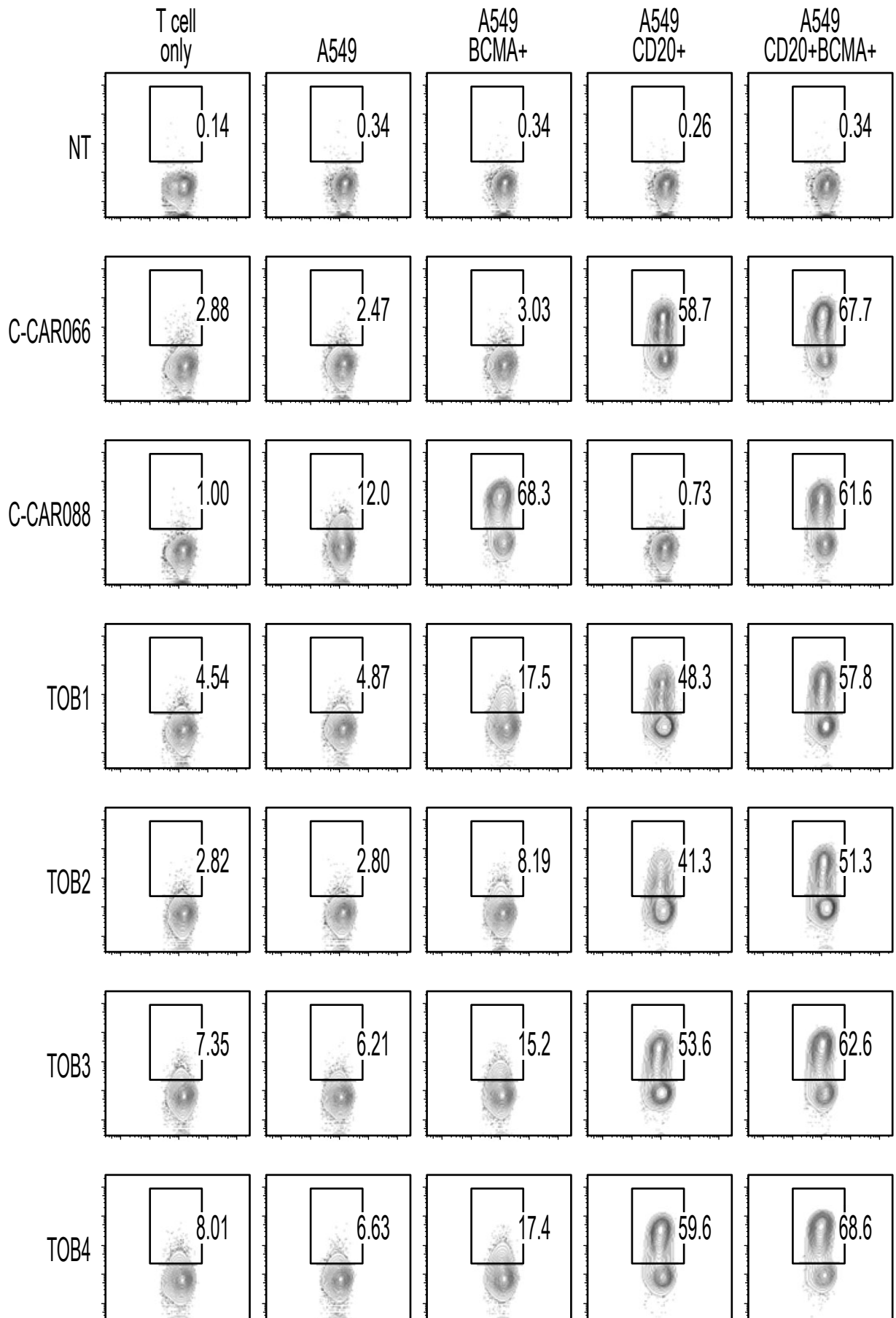


FIG. 4A

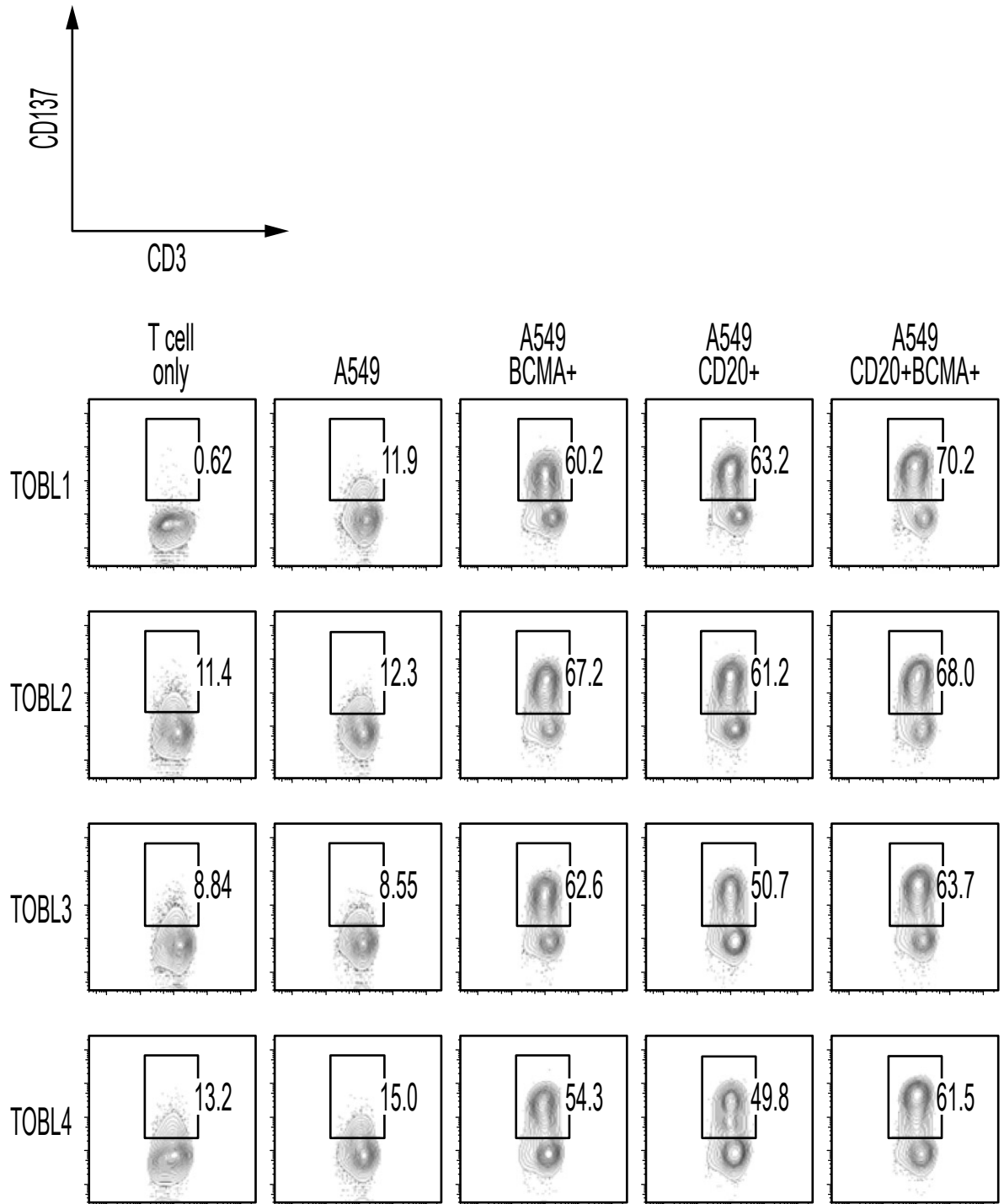


FIG. 4B

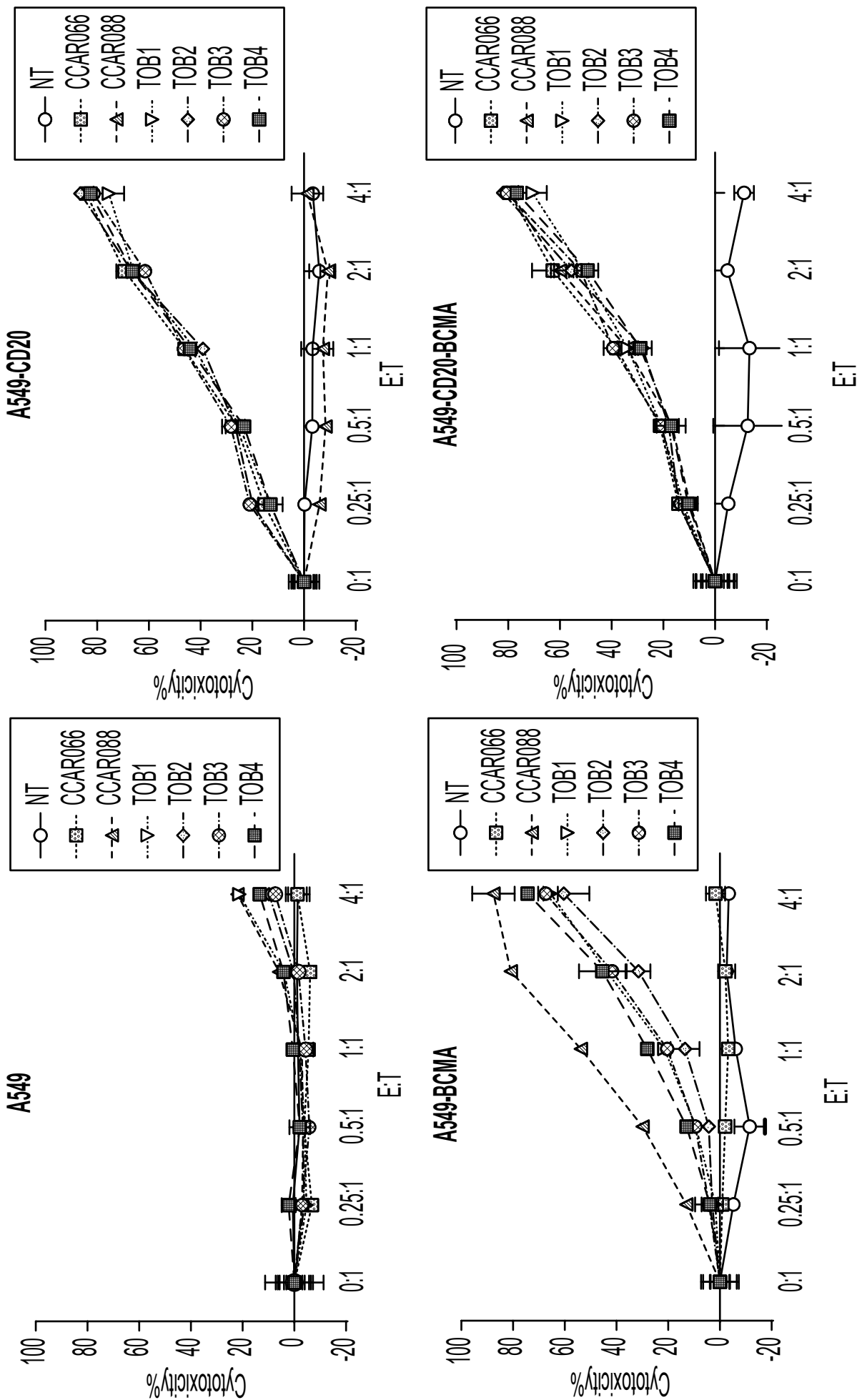


FIG. 5A

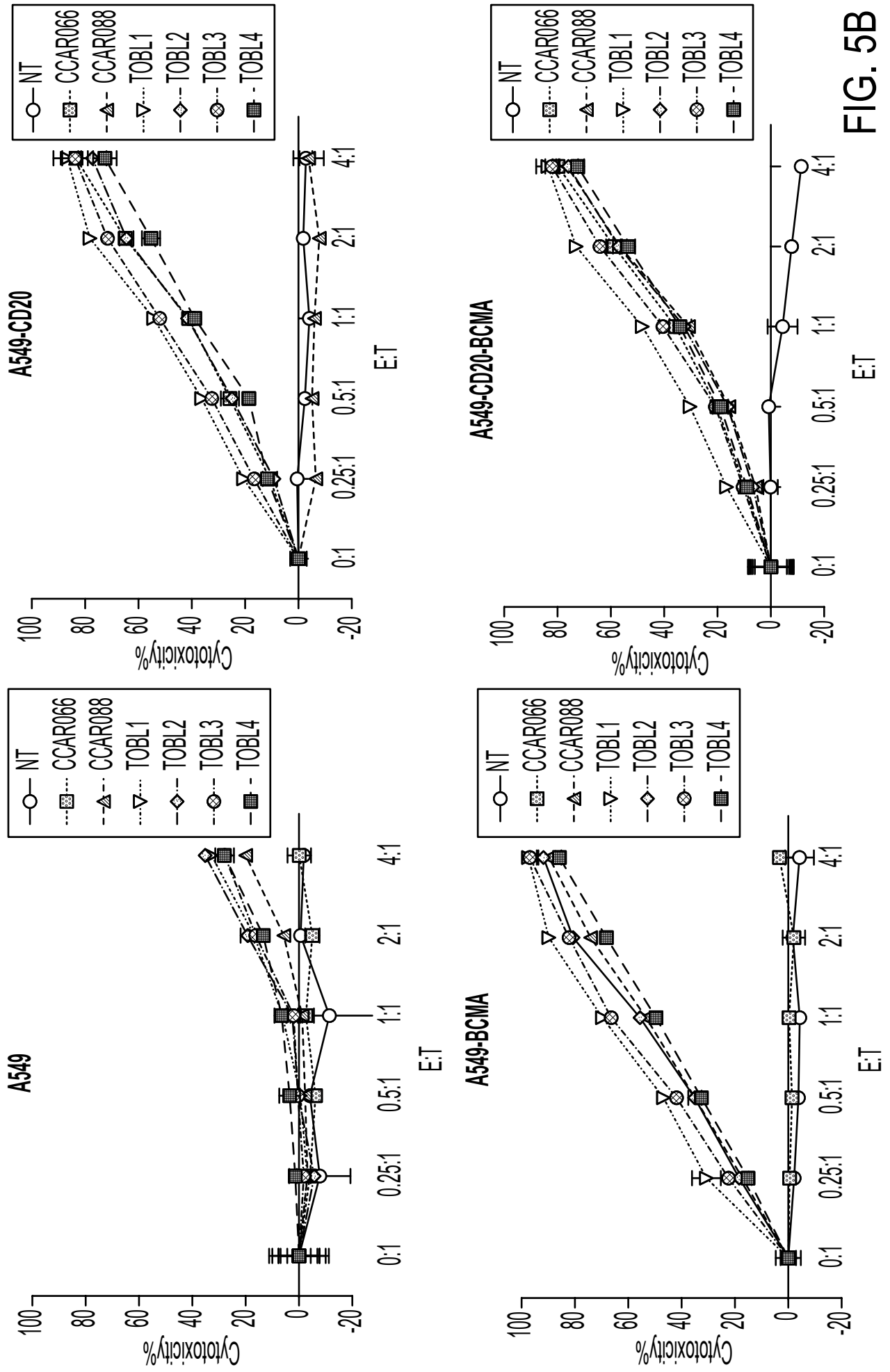


FIG. 5B

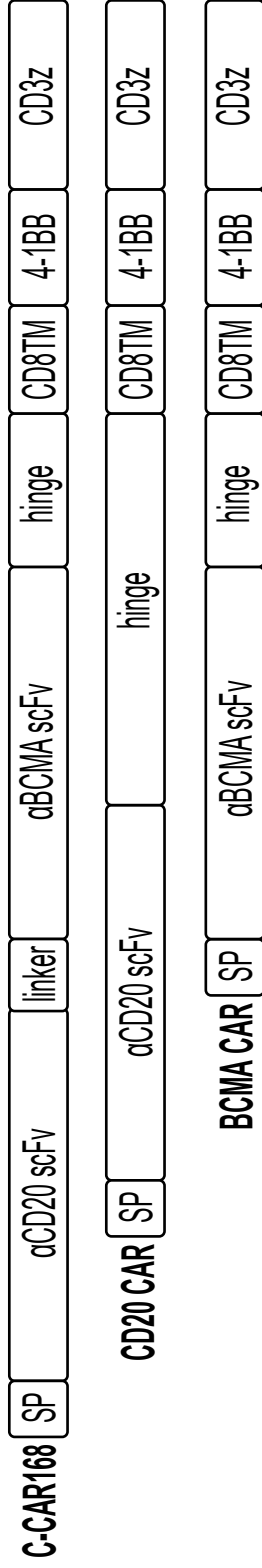


FIG. 6A

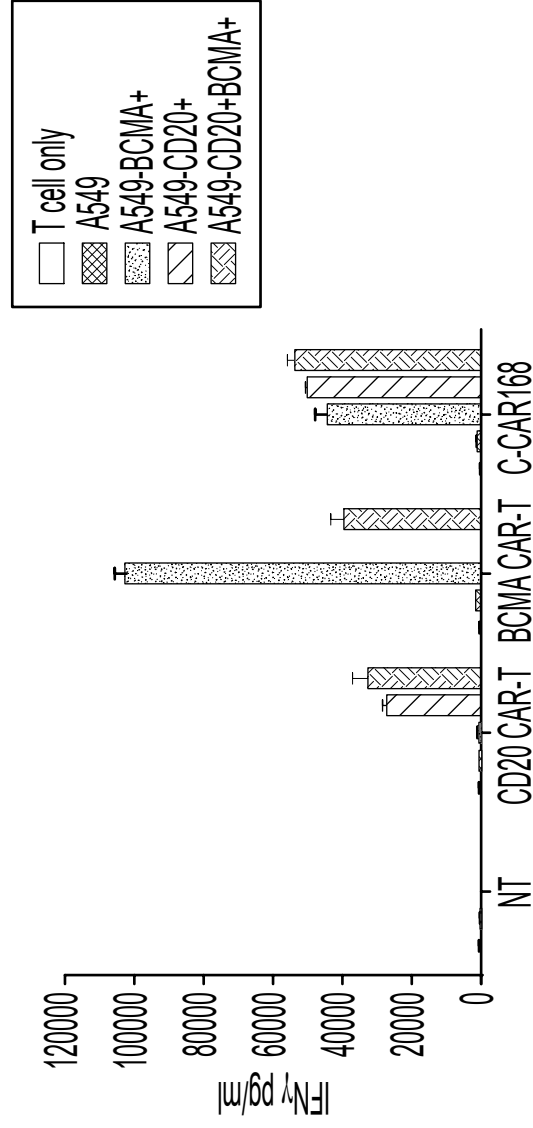


FIG. 6B

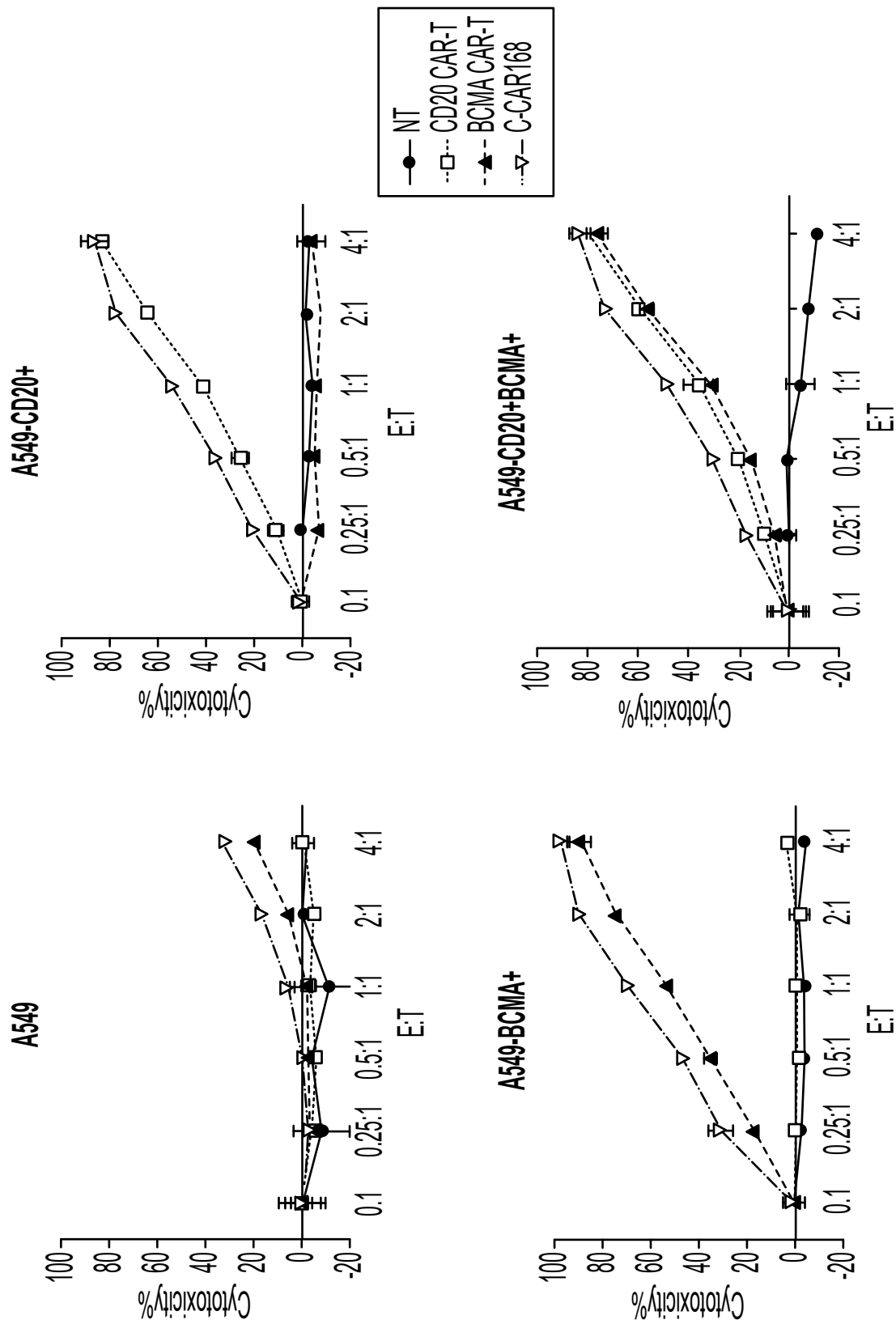


FIG. 6C

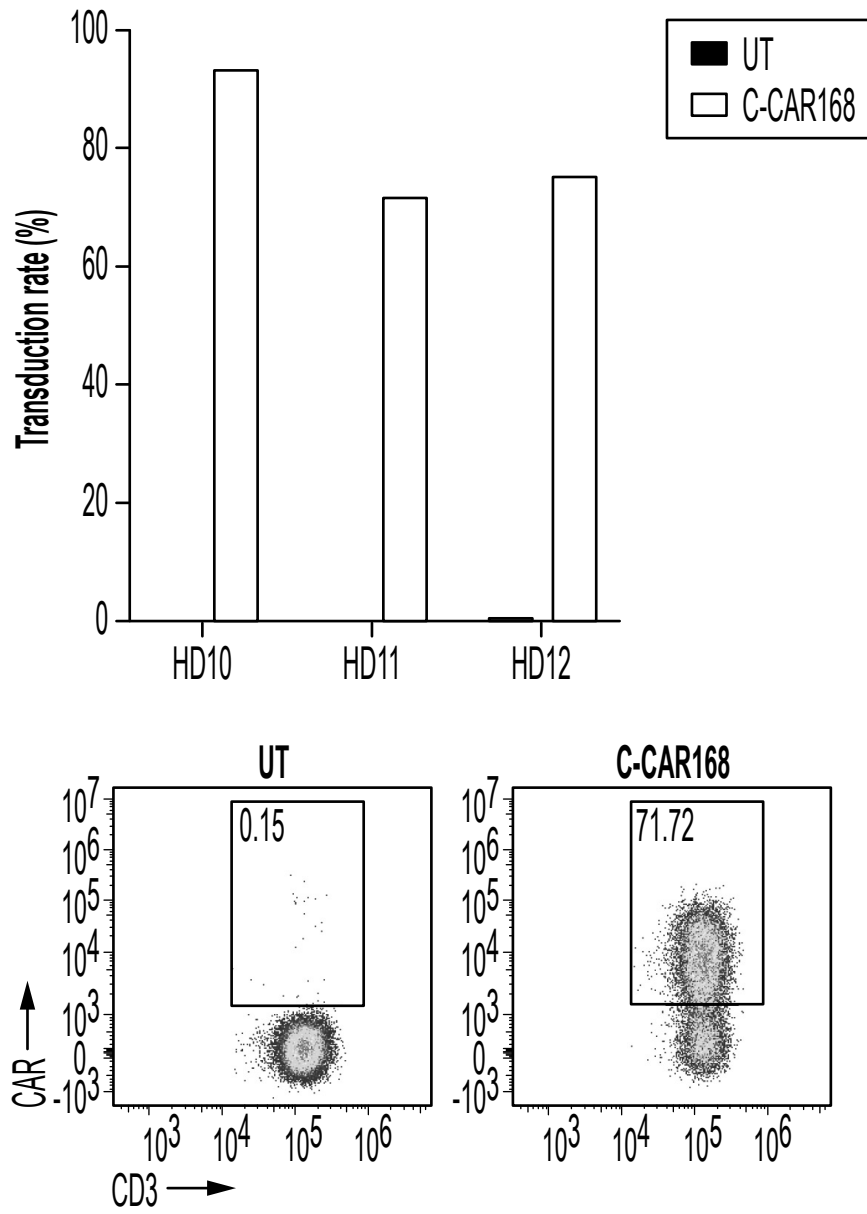


FIG. 7A

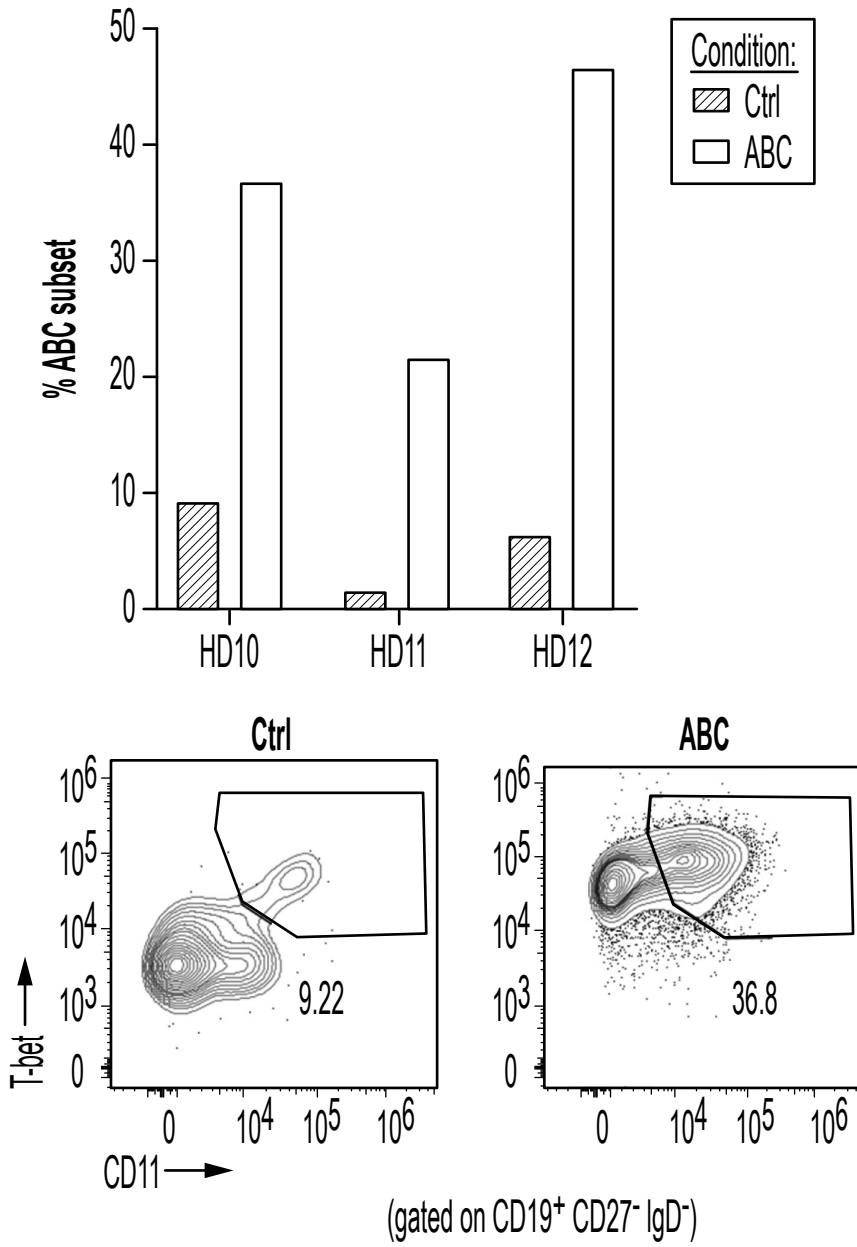


FIG. 7B

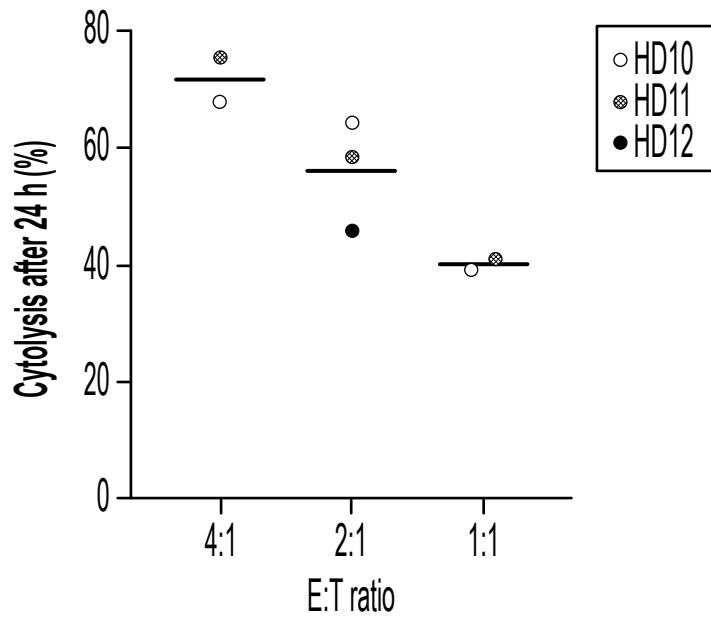
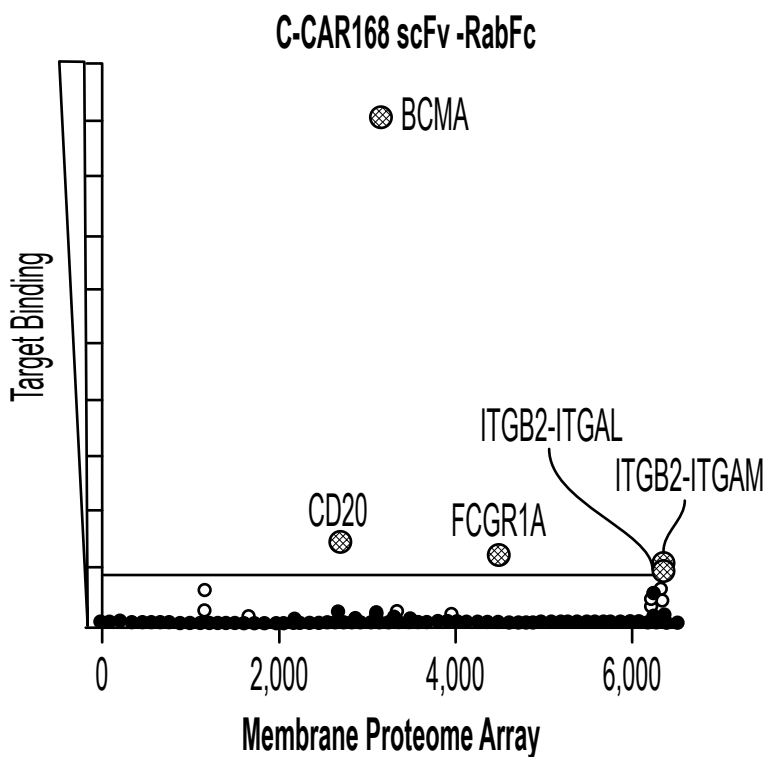
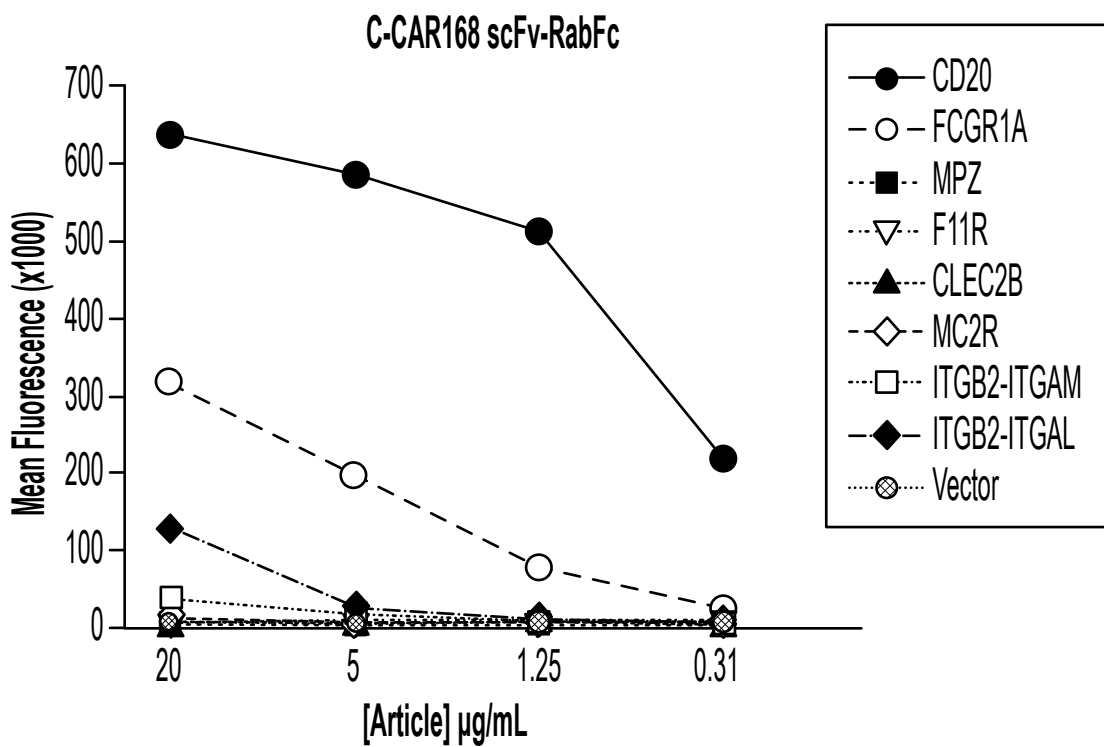


FIG. 7C



**FIG. 8A**



**FIG. 8B**

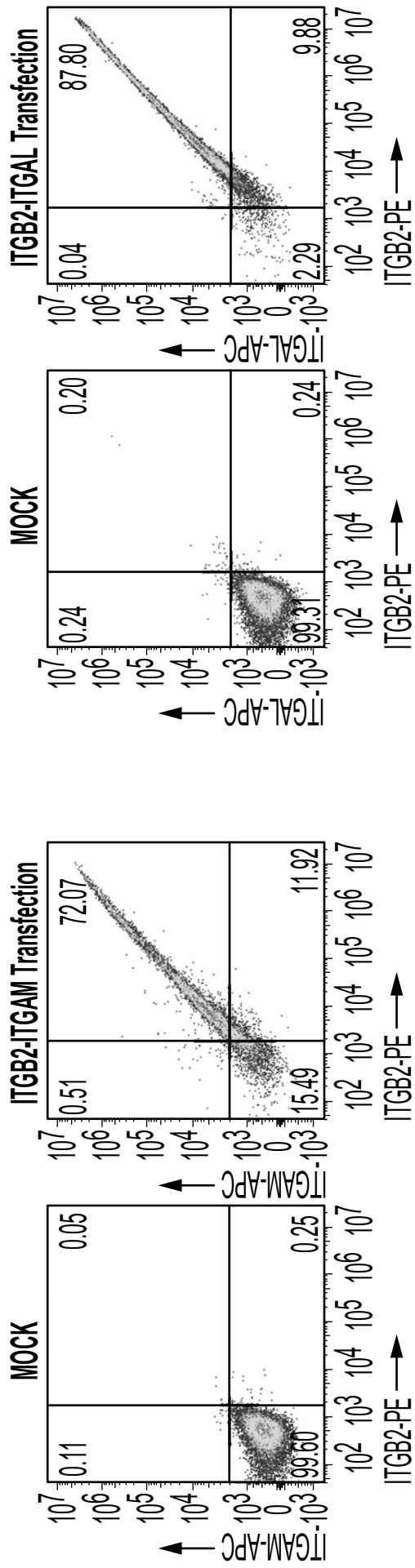


FIG. 8C

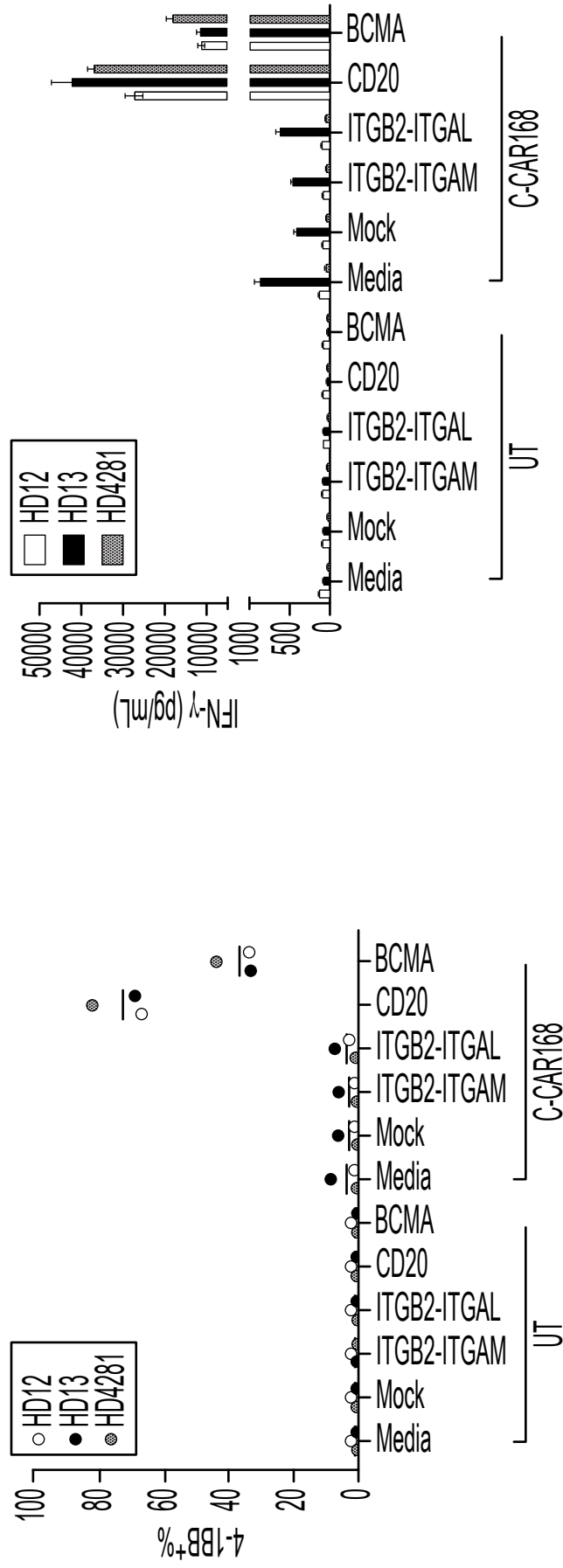


FIG. 8D

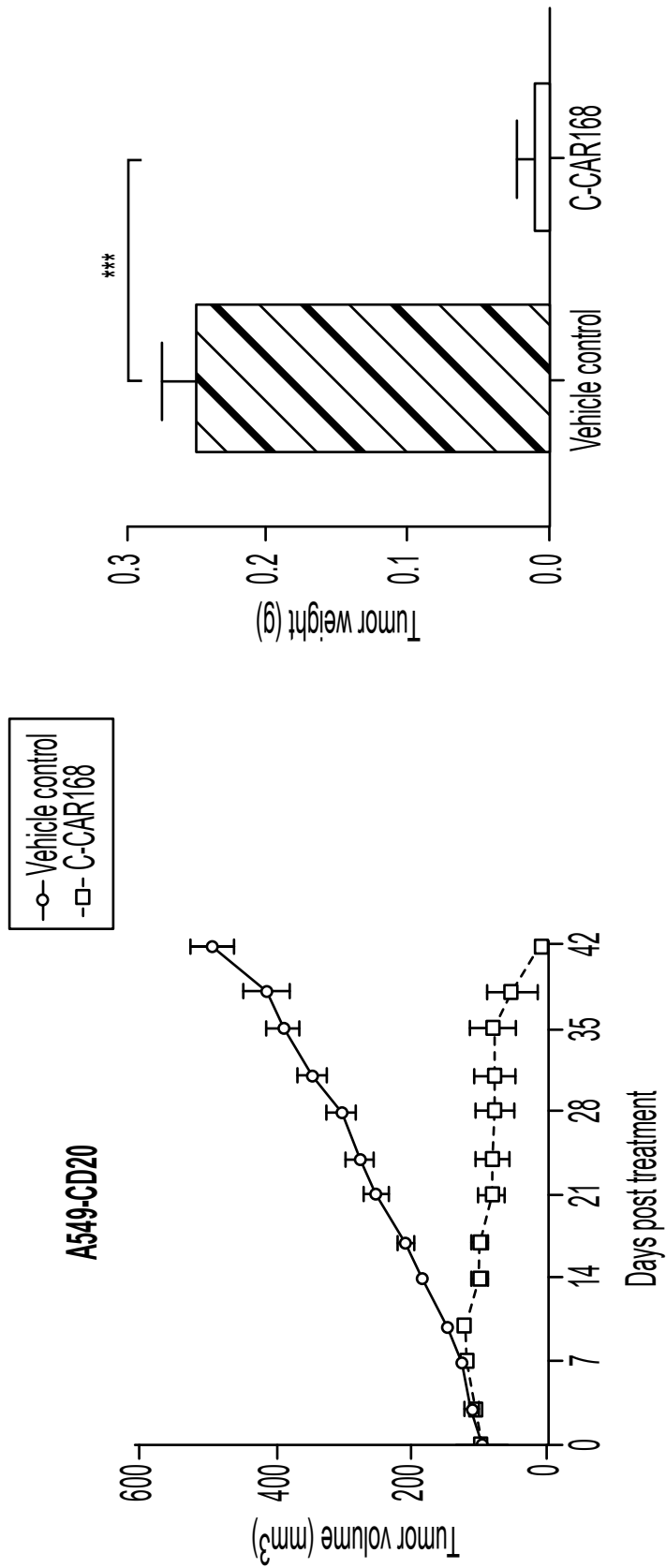


FIG. 9A

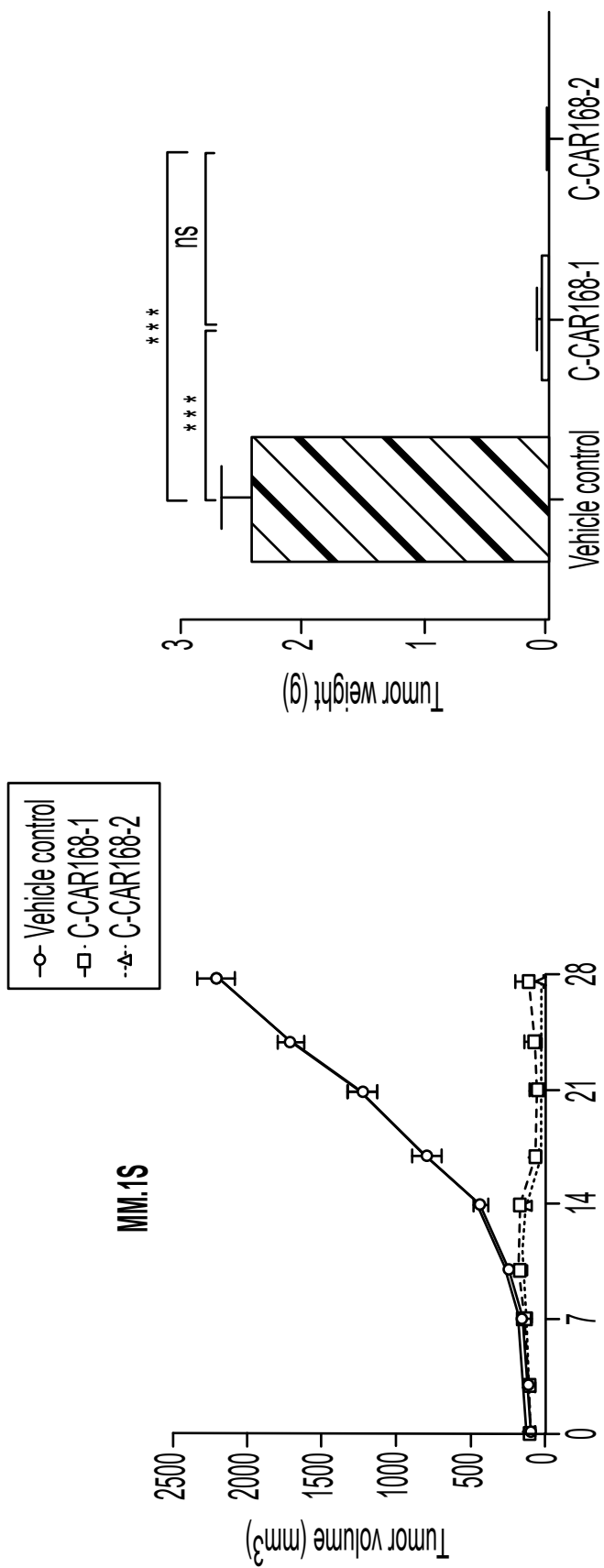


FIG. 9B

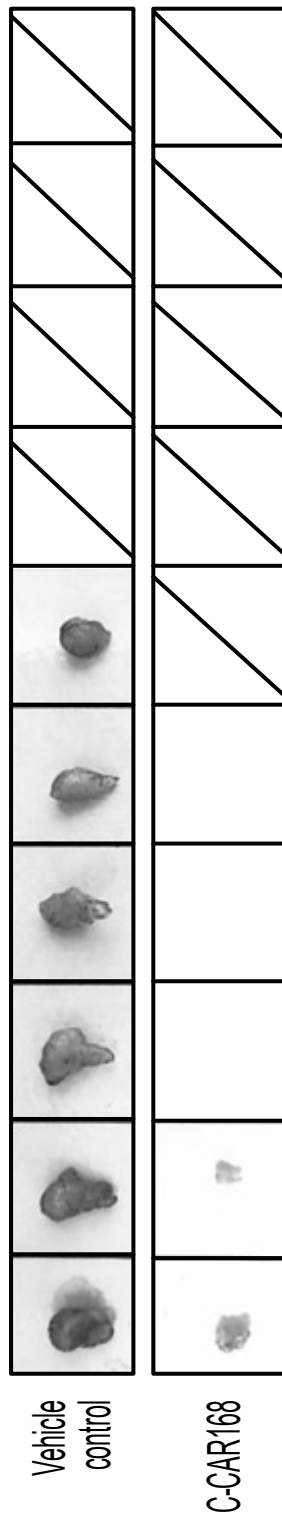


FIG. 9C

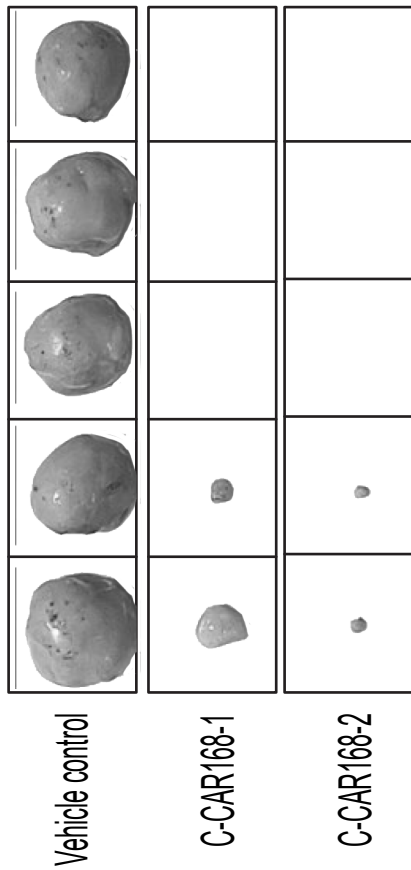


FIG. 9D

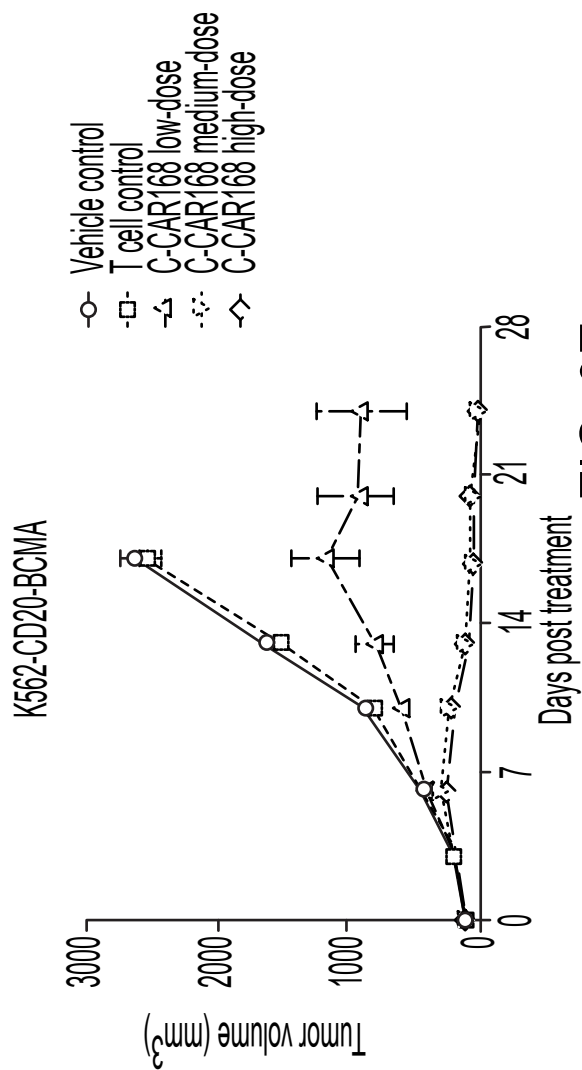


FIG. 9E

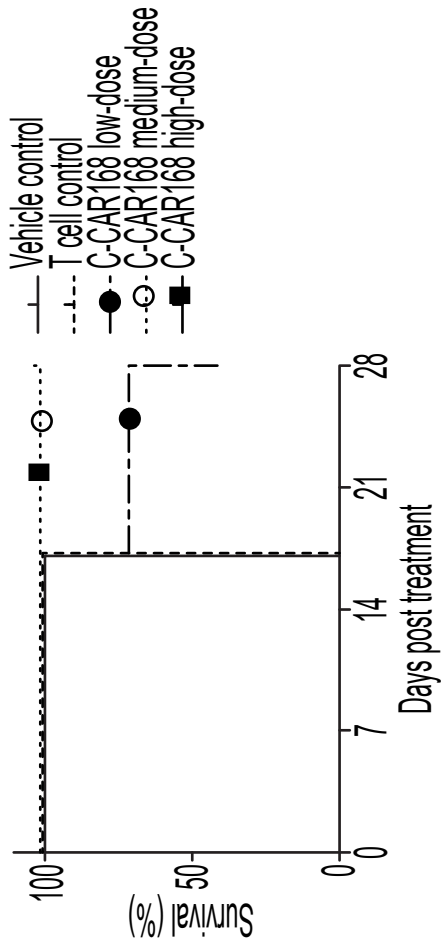


FIG. 9F

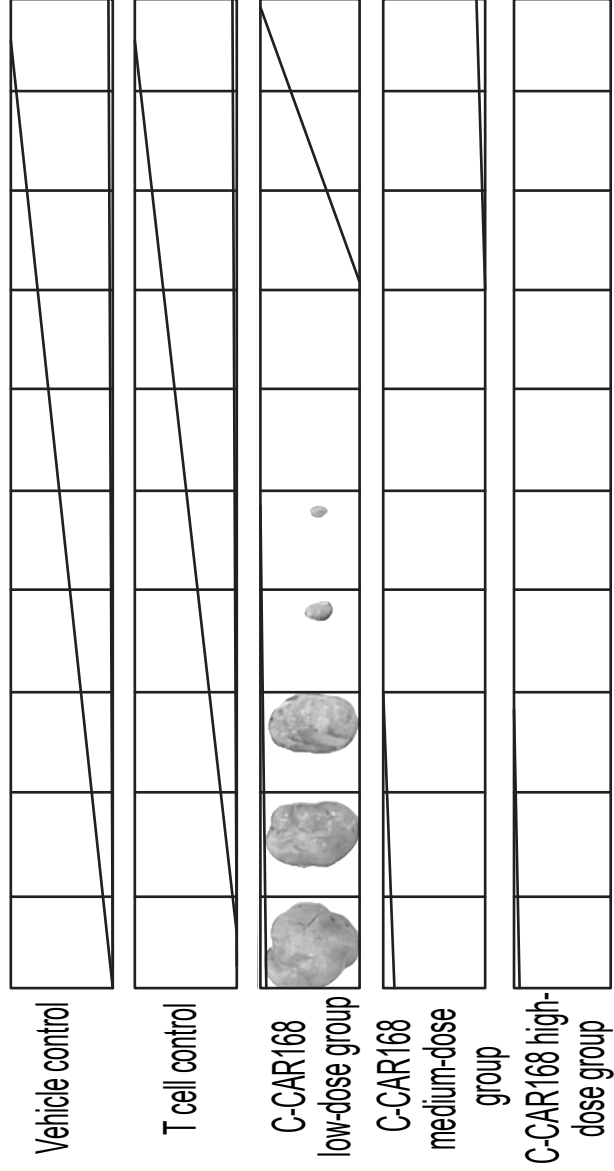


FIG. 9G

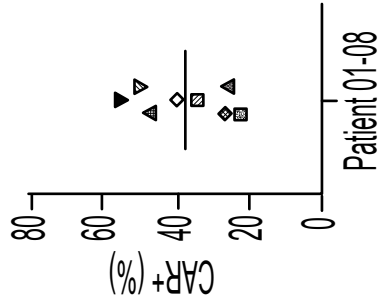


FIG. 10A

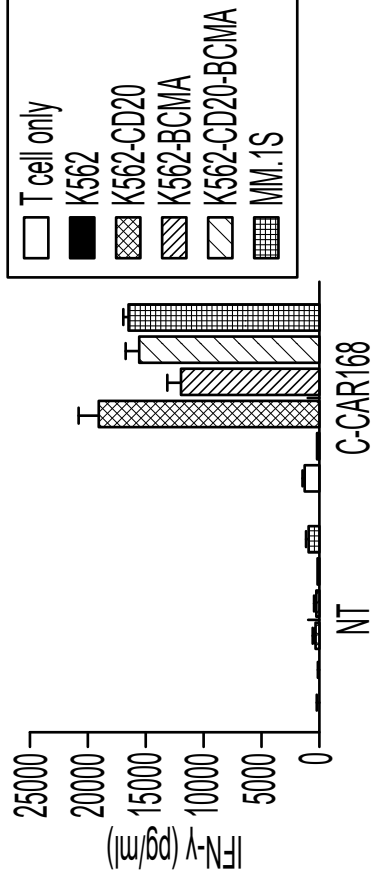


FIG. 10B

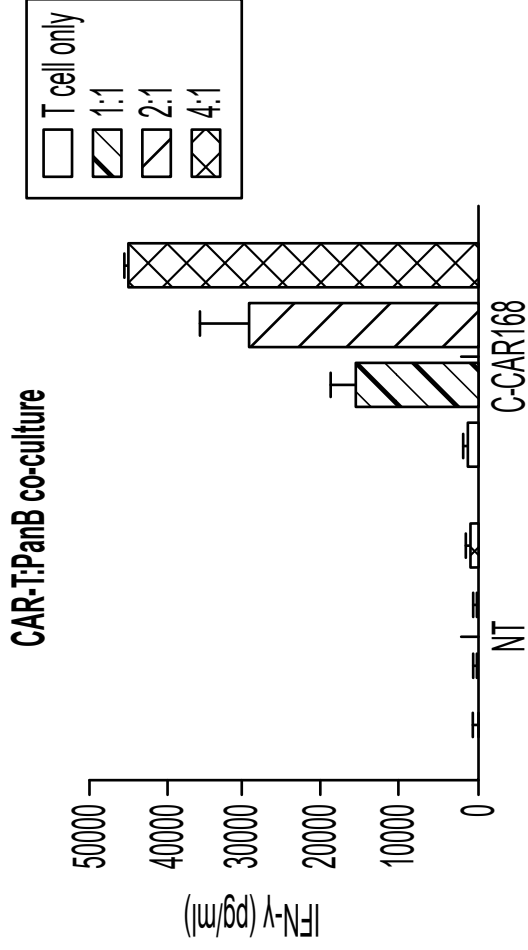


FIG. 10C

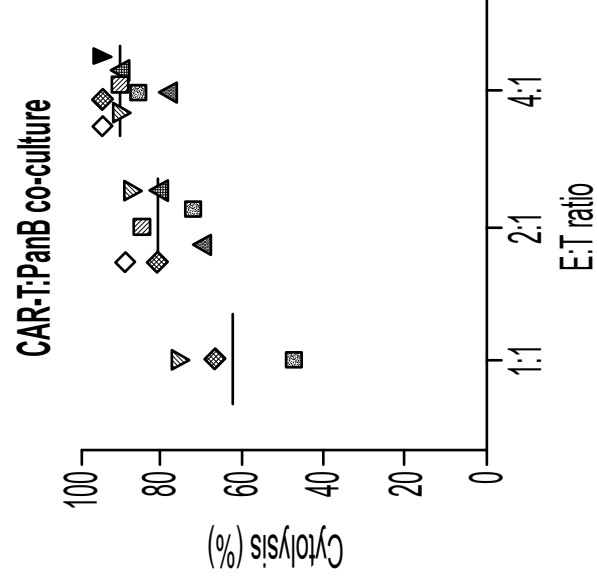


FIG. 10D

# Sequence Listing

26 Feb 2026

2026201441

<b>1</b>	<b>Sequence Listing Information</b>	
1-1	File Name	11299_011840-WO0_SL.xml
1-2	DTD Version	V1_3
1-3	Software Name	WIPO Sequence
1-4	Software Version	2.3.0
1-5	Production Date	2024-03-26
1-6	Original free text language code	
1-7	Non English free text language code	
<b>2</b>	<b>General Information</b>	
2-1	Current application: IP Office	
2-2	Current application: Application number	
2-3	Current application: Filing date	
2-4	Current application: Applicant file reference	11299/011840-WO0
2-5	Earliest priority application: IP Office	US
2-6	Earliest priority application: Application number	63/493,495
2-7	Earliest priority application: Filing date	2023-03-31
2-8en	Applicant name	ABELZETA INC.
2-8	Applicant name: Name Latin	
2-9en	Inventor name	
2-9	Inventor name: Name Latin	
2-10en	Invention title	BISPECIFIC CHIMERIC ANTIGEN RECEPTORS TARGETING CD20 AND BCMA
2-11	Sequence Total Quantity	146

<b>3-1</b>	<b>Sequences</b>	
3-1-1	Sequence Number [ID]	1
3-1-2	Molecule Type	DNA
3-1-3	Length	63
3-1-4	Features	<b>source 1..63</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-1-5	Residues	atggccttac cagtgaccgc ctgtctcctg ccgctggcct tgctgctcca cgccgccagg 60 ccg 63
<b>3-2</b>	<b>Sequences</b>	
3-2-1	Sequence Number [ID]	2
3-2-2	Molecule Type	AA
3-2-3	Length	21
3-2-4	Features	<b>source 1..21</b>
	Location/Qualifiers	mol_type=protein organism=synthetic construct
	NonEnglishQualifier Value	
3-2-5	Residues	MALPVTALLL PLALLLHAAR P 21
<b>3-3</b>	<b>Sequences</b>	
3-3-1	Sequence Number [ID]	3
3-3-2	Molecule Type	DNA
3-3-3	Length	321
3-3-4	Features	<b>source 1..321</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-3-5	Residues	gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccagggga aagagccacc 60 ctctcctgca gggccagtcga gagtgttagc agctacttag cctggtacca acagaacacct 120 ggccaggctc ccaggctcct catctatgat gcatccaaca gggccactgg catcccagcc 180 aggttcagtg gcagtgggtc tgggacagac ttcactctca ccatcagcag cctagagcct 240 gaagattttg cagtttatba ctgtcagcag cgtagcaact ggccgatcac cttcggccaa 300 gggacacgac tggagattaa a 321
<b>3-4</b>	<b>Sequences</b>	
3-4-1	Sequence Number [ID]	4
3-4-2	Molecule Type	AA
3-4-3	Length	107
3-4-4	Features	<b>source 1..107</b>
	Location/Qualifiers	mol_type=protein organism=synthetic construct
	NonEnglishQualifier Value	
3-4-5	Residues	EIVLTQSPAT LSLSPGERAT LSCRASQSVS SYLAWYQQKP GQAPRLLIYD ASNRATGIPA 60 RFSGSGSGTD FTLTISSLEP EDFAVYYCQQ RSNWPITFGQ GTRLEIK 107
<b>3-5</b>	<b>Sequences</b>	
3-5-1	Sequence Number [ID]	5
3-5-2	Molecule Type	DNA
3-5-3	Length	54
3-5-4	Features	<b>source 1..54</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-5-5	Residues	ggcagtaact gcggtggtgg ctccgggggc ggttccggtg ggggcggcag cagc 54
<b>3-6</b>	<b>Sequences</b>	
3-6-1	Sequence Number [ID]	6
3-6-2	Molecule Type	AA
3-6-3	Length	18
3-6-4	Features	<b>source 1..18</b>
	Location/Qualifiers	mol_type=protein organism=synthetic construct
	NonEnglishQualifier Value	
3-6-5	Residues	GSTSGGGSGG GSGGGGSS 18
<b>3-7</b>	<b>Sequences</b>	
3-7-1	Sequence Number [ID]	7
3-7-2	Molecule Type	DNA
3-7-3	Length	366
3-7-4	Features	<b>source 1..366</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	

3-7-5	Residues	gaagtgcagc tggaggagtc tgggggaggc ttggtacagc ctggcaggtc cctgagactc 60 tcctgtgcag cctctggatt cacctttaat gattatgcc a tgcaactgggt cgggcaagct 120 ccaggaagc gcctggagtg ggtctcaact attagttgga atagtggttc catagggat 180 gcgactctg tgaagggccg atccaccatc tccagagaca acgccaagaa gtcctctgat 240 ctgcaaatga acagtctgag agctgaggac acggccttgt attactgtgc aaaagatata 300 cagtacggca actactacta cggtatggac gtctggggcc aagggaccac ggtcaccgtc 360 tcctca 366
3-8	<b>Sequences</b>	
3-8-1	Sequence Number [ID]	8
3-8-2	Molecule Type	AA
3-8-3	Length	122
3-8-4	Features	<b>source 1..122</b>
	Location/Qualifiers	mol_type=protein organism=synthetic construct
	NonEnglishQualifier Value	
3-8-5	Residues	EVQLVESGGG LVQPGRSLRL SCAASGFTFN DYAMHWVRQA PGKGLEWVST ISWNSGSIGY 60 ADSVKGRFTI SRDNAKKSly LQMNSLRAED TALYYCAKDI QYGNYYGMD VWGQGTITVTV 120 SS 122
3-9	<b>Sequences</b>	
3-9-1	Sequence Number [ID]	9
3-9-2	Molecule Type	DNA
3-9-3	Length	15
3-9-4	Features	<b>source 1..15</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-9-5	Residues	ggaggtggtg gatcc 15
3-10	<b>Sequences</b>	
3-10-1	Sequence Number [ID]	10
3-10-2	Molecule Type	AA
3-10-3	Length	5
3-10-4	Features	<b>source 1..5</b>
	Location/Qualifiers	mol_type=protein organism=synthetic construct
	NonEnglishQualifier Value	
3-10-5	Residues	GGGGS 5
3-11	<b>Sequences</b>	
3-11-1	Sequence Number [ID]	11
3-11-2	Molecule Type	DNA
3-11-3	Length	321
3-11-4	Features	<b>source 1..321</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-11-5	Residues	gacatccaga tgaccagtc ccctcctcc ctgtccgct ccgtgggcga cgggtgacc 60 atcacctgcc gggcctccca gggcatctcc aactacctga actggtacca gcagaagccc 120 ggcaaggccc ccaagcccct gatctactac acctccaacc tgcagtcgg cgtgccctcc 180 cggttctccg gctccggctc cggcaccgac tacacctga ccatctctc cctgcagccc 240 gaggacttcg ccacctacta ctgcatgggc cagaccatct cctcctacac ctctggccag 300 ggcaccaagc tggagatcaa g 321
3-12	<b>Sequences</b>	
3-12-1	Sequence Number [ID]	12
3-12-2	Molecule Type	AA
3-12-3	Length	107
3-12-4	Features	<b>source 1..107</b>
	Location/Qualifiers	mol_type=protein organism=synthetic construct
	NonEnglishQualifier Value	
3-12-5	Residues	DIQMTQSPSS LSASVGRVIT ITCRASQGIS NYLNWYQKP GKAPKPLIYY TSNLQSGVPS 60 RFGSGSGTDT YTLTISSLQP EDFATYYCMG QTISSYTFGQ GTKLEIK 107
3-13	<b>Sequences</b>	
3-13-1	Sequence Number [ID]	13
3-13-2	Molecule Type	DNA
3-13-3	Length	45
3-13-4	Features	<b>source 1..45</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-13-5	Residues	ggtggcggtg gctcgggcgg tgggtggctg ggtggcggcg gatct 45
3-14	<b>Sequences</b>	

3-14-1	Sequence Number [ID]	14
3-14-2	Molecule Type	AA
3-14-3	Length	15
3-14-4	Features	<b>source 1..15</b>
	Location/Qualifiers	mol_type=protein organism=synthetic construct
	NonEnglishQualifier Value	
3-14-5	Residues	GGGSGGGGS GGGGS 15
<b>3-15</b>	<b>Sequences</b>	
3-15-1	Sequence Number [ID]	15
3-15-2	Molecule Type	DNA
3-15-3	Length	363
3-15-4	Features	<b>source 1..363</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-15-5	Residues	gaggtgcagc tggtagtgc cggcgccggc ctggtgcagc cggcgccgctc cctgcggctg 60 tcctgcgccc cctccggctt caccttctcc aacttcgaca tggcctgggt gcggcaggcc 120 cccggcaagg gctggtgtg ggtgtctctc atcaccaccg gcgcccacca cgccatctac 180 gccgactccg tgaagggccg gttcaccatc tcccgggaca acgccaagaa cacctgtac 240 ctgcagatga actccctcgg gcccgaggac accgcccgtg actactgcgt gcggcacggc 300 tactacgacg gctaccacct gttcgactac tggggccagg gcaccctggt gaccgtgtcc 360 tcc 363
<b>3-16</b>	<b>Sequences</b>	
3-16-1	Sequence Number [ID]	16
3-16-2	Molecule Type	AA
3-16-3	Length	121
3-16-4	Features	<b>source 1..121</b>
	Location/Qualifiers	mol_type=protein organism=synthetic construct
	NonEnglishQualifier Value	
3-16-5	Residues	EVQLVESGGG LVQPGGSLRL SCAASGFTFS NFDMAWVRQA PGKGLVWVSS ITTGADHAIY 60 ADSVKGRFTI SRDNAKNTLY LQMNSLRAED TAVYYCVRHG YYDGYHLFDY WGQGLVTVS 120 S 121
<b>3-17</b>	<b>Sequences</b>	
3-17-1	Sequence Number [ID]	17
3-17-2	Molecule Type	DNA
3-17-3	Length	165
3-17-4	Features	<b>source 1..165</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-17-5	Residues	ttcgtgccgg tcttctctgcc agcgaagccc accacgacgc cagcgccgcg accaccaaca 60 ccggcgccca ccacgcgctc gcagcccctg tccctgcgcc cagaggcgtg ccggccagcg 120 gcggggggcg cagtgcacac gagggggctg gacttcgctc gtgat 165
<b>3-18</b>	<b>Sequences</b>	
3-18-1	Sequence Number [ID]	18
3-18-2	Molecule Type	AA
3-18-3	Length	55
3-18-4	Features	<b>source 1..55</b>
	Location/Qualifiers	mol_type=protein organism=synthetic construct
	NonEnglishQualifier Value	
3-18-5	Residues	FVPVFLPAKP TTPAPRPT PAPTIASQPL SLRPEACRPA AGGAVHTRGL DFACD 55
<b>3-19</b>	<b>Sequences</b>	
3-19-1	Sequence Number [ID]	19
3-19-2	Molecule Type	DNA
3-19-3	Length	72
3-19-4	Features	<b>source 1..72</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-19-5	Residues	atctacatct gggcgccctt gccgggact tgtggggctc ttctctctgc actggttacc 60 acccttact gc 72
<b>3-20</b>	<b>Sequences</b>	
3-20-1	Sequence Number [ID]	20
3-20-2	Molecule Type	AA
3-20-3	Length	24
3-20-4	Features	<b>source 1..24</b>

	Location/Qualifiers	mol_type=protein organism=synthetic construct	
3-20-5	NonEnglishQualifier Value Residues	IYIWAPLAGT CGVLLLSLVI TLYC	24
<b>3-21</b>	<b>Sequences</b>		
3-21-1	Sequence Number [ID]	21	
3-21-2	Molecule Type	DNA	
3-21-3	Length	126	
3-21-4	Features	<b>source 1..126</b>	
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct	
3-21-5	NonEnglishQualifier Value Residues	aaacggggca gaaagaaact cctgtatata ttcaaacaac catttatgag accagtacaa 60 actactcaag aggaagatgg ctgtagctgc cgatttccag aagaagaaga aggaggatgt 120 gaactg 126	
<b>3-22</b>	<b>Sequences</b>		
3-22-1	Sequence Number [ID]	22	
3-22-2	Molecule Type	AA	
3-22-3	Length	42	
3-22-4	Features	<b>source 1..42</b>	
	Location/Qualifiers	mol_type=protein organism=synthetic construct	
3-22-5	NonEnglishQualifier Value Residues	KRGRKLLLYI FKQPFMRPVQ TTQEEDGCSC RFPEEEEGGC EL	42
<b>3-23</b>	<b>Sequences</b>		
3-23-1	Sequence Number [ID]	23	
3-23-2	Molecule Type	DNA	
3-23-3	Length	339	
3-23-4	Features	<b>source 1..339</b>	
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct	
3-23-5	NonEnglishQualifier Value Residues	agagtgaagt tcagcaggag cgcagacgcc cccgcgtacc agcagggcca gaaccagctc 60 tataacgagc tcaatctagg acgaagagag gactacgatg ttttggacaa gagacgtggc 120 cgggaccctg agatgggggg aaagccgaga aggaagaacc ctcaggaagg cctgtacaat 180 gaactgcaga aagataagat ggcggaggcc tacagtgaga ttgggatgaa aggcgagcgc 240 cggaggggca aggggcacga tggcctttac cagggctcga gtacagccac caaggacacc 300 tacgacgccc ttcacatgca ggcctctgcc cctcgctaa 339	
<b>3-24</b>	<b>Sequences</b>		
3-24-1	Sequence Number [ID]	24	
3-24-2	Molecule Type	AA	
3-24-3	Length	112	
3-24-4	Features	<b>source 1..112</b>	
	Location/Qualifiers	mol_type=protein organism=synthetic construct	
3-24-5	NonEnglishQualifier Value Residues	RVKFSRSADA PAYQQGQNL YNELNLGRRE EYDVLDKRRG RDPENGGKPR RKNPQEGLYN 60 ELQKDKMAEA YSEIGMKGER RRGKGDHGLY QGLSTATKDT YDALHMQUALP PR 112	
<b>3-25</b>	<b>Sequences</b>		
3-25-1	Sequence Number [ID]	25	
3-25-2	Molecule Type	DNA	
3-25-3	Length	2250	
3-25-4	Features	<b>source 1..2250</b>	
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct	
3-25-5	NonEnglishQualifier Value Residues	atggccttac cagtgaccgc cttgctcctg ccgctggcct tgctgctcca cgccgccagg 60 ccggaaattg tgttgacaca gtctccagcc accctgtctt tgtctccagg ggaaagagcc 120 accctctcct gcagggccag tcagagtgtt agcagctact tagcctggta ccaacagaaa 180 cctggccagg ctcccaggct cctcatctat gatgcatcca acagggccac tggcatocca 240 gccaggttca gtggcagtgg gtctgggaca gacttcactc tcaccatcag cagcctagag 300 cctgaagatt ttgcagtta ttactgtcag cagcgtagca actggccgat caccttcggc 360 caagggacac gactggagat taaaggcagt actagcgggt gtggctccgg gggcggttcc 420 ggtgggggcg gcagcagcga agtgcagctg gtggagtctg ggggaggcct ggtacagcct 480 ggcagggtccc tgagactctc ctgtgcagcc tctggattca cctttaatga ttatgccatg 540 cactgggtcc ggcaagctcc aggaagggc ctggagtggg tctcaactat tagttggaat 600 agtggttcca taggctatgc ggactctgtg aagggccgat tcaccatctc cagagacaac 660 gccagaagt cctgtatct gcaaatgaac agtctgagag ctgaggacac ggccttgtat 720 tactgtgcaa aagatataca gtacggcaac tactactacg gtatggacgt ctggggccaa 780 gggaccacgg tcaccgtctc ctcaggaggt ggtggatccg acatccagat gaccacagtc 840	

		<pre> ccctoctccc tgtccgctc cgtgggcgac cgggtgacca tcacctgccg ggcctcccag 900 ggcatctcca actacctgaa ctggtaccag cagaagcccc gcaaggcccc caagcccctg 960 atctactaca cctccaacct gcagtcggcg gtgccctccc ggttctccgg ctcccggctc 1020 ggcaccgact acaccctgac catctcctcc ctgcagcccc aggactctgc cacctactac 1080 tgcattgggccc agaccatctc ctccatcacc ttcggccagg gcaccaagct ggagatcaag 1140 ggtggcggtg gctcggggcg tgggtgggtcg ggtggcgggc gatctgaggt gcagctggtg 1200 gagtcggcg ggcgctggt gcagccccgc ggctcctgc ggctgtcctg cggcgctcc 1260 ggcttcacct tctccaactt cgactggccc tgggtgcgcc agggccccgg caaggcctg 1320 gtgtgggtgt cctccatcac caccggcgcc gaccacgcca tctacgccga ctccgtgaag 1380 ggccggttca ccatctcccg ggacaacgcc aagaacacct tgtacctgca gatgaactcc 1440 ctgcgggccc aggacaccgc cgtgtaactac tgcgtgccc acggctacta cgacggctac 1500 cactgttctg actactgggg ccagggcacc ctggtgaccg tgcctcctt cgtgcccgtc 1560 ttcctgccag cgaagcccac cagcagccca gcgcgcgac caccaacacc ggcgcccacc 1620 atcgcgtcgc agcccctgtc cctgcgccc gaggcgtgcc ggccagcgcc gggggcgca 1680 gtgcacacga ggggctgga cttcgctgt gatattaca tctggcgccc ctggcggg 1740 acttggggg tcttctctc gtcactggtt atcaccttt actgcaaacg gggcagaaa 1800 aaactcctgt atatattcaa acaaccattt atgagaccag taaaaactac tcaagaggaa 1860 gatggctgta gtcgcccatt tccagaagaa gaagaaggag gatgtgaact gagagtgaag 1920 ttcagcagga gcgagcagc ccccgctac cagcagggcc agaaccagct ctataacgag 1980 ctcaatctag gacgaagaga ggagtagat gttttggaca agagacgtgg ccgggaccct 2040 gagatgggg gaaagccgag aaggaagaac cctcaggaag gcctgtacaa tgaactgca 2100 aaagataaga tggcggaggc ctacagtgag attgggatga aaggcgagcg ccggaggggc 2160 aaggggcacg atggccttta ccagggtctc agtacagcca ccaaggacac ctacgagccc 2220 cttcacatgc aggcctgcc cctcgcgtaa 2250 </pre>
3-26	<b>Sequences</b>	
3-26-1	Sequence Number [ID]	26
3-26-2	Molecule Type	AA
3-26-3	Length	749
3-26-4	Features	<b>source 1..749</b>
	Location/Qualifiers	mol_type=protein organism=synthetic construct
	NonEnglishQualifier Value	
3-26-5	Residues	<pre> MALPVTALLL PLALLLHAAR PEIVLTQSPA TLSLSPGERA TLSCRASQSV SSYLAWYQQK 60 PGQAPRLLIY DASNRATGIP ARFSGSGSGT DFTLTISSLE PEDFAVYQC QRSNWPITFG 120 QGTRLEIKGS TSGGSGGGS GGGGSSEVQL VESGGGLVQP GRSLRLSCAA SGFTFNDYAM 180 HWVRQAPGKG LEWVSTISWN SGSIGYADSV KGRFTISRDN AKKSLYLQMN SLRAEDTALY 240 YCAKDIQYGN YYGMDVWQ GTTVTVSSGG GSDIQMTQS PSSLSASVDG RVTITCRASQ 300 GISNYLNWYQ QKPGKAPKPL IYYSNLQSG VPSRFSGSGS GTDYTLTISS LQPEDFATYY 360 CMGQTISSYT FGQGTKLEIK GGGGSGGGS GGGGSEVQLV ESGGGLVQPG GSLRLSCAAS 420 GFTFSNFDMA WVRQAPGKGL VWVSSIITGA DHAIYADSVK GRFTISRDN KNTLYLQMNS 480 LRAEDTAVY CVRHGYDGY HLFDYWGQGT LVTVSSFVPV FLPAKPTTTP APRPPTPAPT 540 IASQPLSLRP EACRPAAGGA VHTRGLDFAC DIYIWAPLAG TCGVLLLSLV ITLYCKRGRK 600 KLLYIFKQPF MRPVQTTQEE DGCSCRFPEE EGGCELRVK FRSADAPAY QQGQNQLYNE 660 LNLGRREEYD VLDKRRGRDP EMGKPRRKN PQEGLYNELQ KDKMAEAYSE IGMKGERRR 720 KGHDGLYQGL STATKDTYDA LHMQUALPPR 749 </pre>
3-27	<b>Sequences</b>	
3-27-1	Sequence Number [ID]	27
3-27-2	Molecule Type	DNA
3-27-3	Length	63
3-27-4	Features	<b>source 1..63</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-27-5	Residues	<pre> atggccttac cagtgaccgc ctgctcctg ccgctggcct tgctgctcca cgccgccagg 60 ccg 63 </pre>
3-28	<b>Sequences</b>	
3-28-1	Sequence Number [ID]	28
3-28-2	Molecule Type	DNA
3-28-3	Length	366
3-28-4	Features	<b>source 1..366</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-28-5	Residues	<pre> gaagtgcagc tgggtggagtc tgggggaggc ttggtacagc ctggcaggtc cctgagactc 60 tcctgtgcag cctctggatt cacctttaat gattatgcca tgcactgggt ccggcaagct 120 ccagggaaag gcctggagtg ggtctcaact attagttgga atagtggttc cataggctat 180 gcggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa gtcctctgtat 240 ctgcaaatga acagtctgag agctgaggac acggccttgt attactgtgc aaaagatata 300 cagtacggca actactacta cggtatggac gtctggggcc aagggaccac ggtcaccgctc 360 tcctca 366 </pre>
3-29	<b>Sequences</b>	
3-29-1	Sequence Number [ID]	29
3-29-2	Molecule Type	DNA

3-29-3	Length	54
3-29-4	Features	<b>source 1..54</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-29-5	Residues	ggcagtacta gcggtggtgg ctccgggggc ggttccggtg ggggcggcag cagc 54
<b>3-30</b>	<b>Sequences</b>	
3-30-1	Sequence Number [ID]	30
3-30-2	Molecule Type	DNA
3-30-3	Length	321
3-30-4	Features	<b>source 1..321</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-30-5	Residues	gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccagggga aagagccacc 60 ctctcctgca gggccagtc gagtgtagc agctacttag cctggtacca acagaaacct 120 ggccaggctc ccaggctcct catctatgat gcatccaaca gggccactgg catcccagcc 180 aggttcagtg gcagtgggtc tgggacagac ttcaacttca ccatcagcag cctagagcct 240 gaagattttg cagtttatta ctgtcagcag cgtagcaact ggccgatcac cttcggccaa 300 gggacacgac tggagattaa a 321
<b>3-31</b>	<b>Sequences</b>	
3-31-1	Sequence Number [ID]	31
3-31-2	Molecule Type	DNA
3-31-3	Length	15
3-31-4	Features	<b>source 1..15</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-31-5	Residues	ggagggtggtg gatcc 15
<b>3-32</b>	<b>Sequences</b>	
3-32-1	Sequence Number [ID]	32
3-32-2	Molecule Type	DNA
3-32-3	Length	321
3-32-4	Features	<b>source 1..321</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-32-5	Residues	gacatccaga tgaccagtc cccctcctcc ctgtccgctt ccgtggggca ccgggtgacc 60 atcacctgcc gggcctcca gggcatctcc aactacctga actggtacca gcagaagccc 120 ggcaaggccc ccaagccctt gatctactac acctccaacc tgcagtcocgg cgtgcctccc 180 cggttctccg gctccggctc cggcaccgac tacacctga ccatctcttc cctgcagccc 240 gaggacttcg ccacctacta ctgcatgggc cagaccatct cctcctacac cttcggccag 300 ggcaccaagc tggagatcaa g 321
<b>3-33</b>	<b>Sequences</b>	
3-33-1	Sequence Number [ID]	33
3-33-2	Molecule Type	DNA
3-33-3	Length	45
3-33-4	Features	<b>source 1..45</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-33-5	Residues	ggtggcggtg gctcgggagg tgggtgggtcg ggtggcggcg gatct 45
<b>3-34</b>	<b>Sequences</b>	
3-34-1	Sequence Number [ID]	34
3-34-2	Molecule Type	DNA
3-34-3	Length	363
3-34-4	Features	<b>source 1..363</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-34-5	Residues	gaggtgacgc tgggtggagtc cggcgggggc ctggtgcagc ccggcggtct cctgcggctg 60 tcctgcgcgc cctccggctt caccttctcc aacttcgaca tggcctgggt gcggcaggcc 120 cccggcaagg gcctggtgtg ggtgtcctcc atcaccaccg gcgccacca cgccatctac 180 gccgactccg tgaagggccg gttcaccatc tcccgggaca acgccaagaa caccctgtac 240 ctgcagatga actccctgcg ggccgaggac accgocgtgt actactgctg gcggcacggc 300 tactacgaag gctaccacct gttcgactac tggggccagg gcacctgggt gaccgtgtcc 360 tcc 363
<b>3-35</b>	<b>Sequences</b>	
3-35-1	Sequence Number [ID]	35
3-35-2	Molecule Type	DNA

3-35-3	Length	165
3-35-4	Features Location/Qualifiers	<b>source 1..165</b> mol_type=other DNA organism=synthetic construct
3-35-5	NonEnglishQualifier Value Residues	ttcgtgccgg tcttctgcc agcgaagccc accacgacgc cagcgccgcg accaccaaca 60 ccggcgccca ccacgcgctc gcagccctcg tcctctgcc cagaggcgtg ccggccagcg 120 gcgggggcg cagtgcacac gagggggctg gacttcgctt gtgat 165
<b>3-36</b>	<b>Sequences</b>	
3-36-1	Sequence Number [ID]	36
3-36-2	Molecule Type	DNA
3-36-3	Length	72
3-36-4	Features Location/Qualifiers	<b>source 1..72</b> mol_type=other DNA organism=synthetic construct
3-36-5	NonEnglishQualifier Value Residues	atctacatct gggcgccctt ggccgggact tgtggggctc tctctctgct actggttatc 60 accctttact gc 72
<b>3-37</b>	<b>Sequences</b>	
3-37-1	Sequence Number [ID]	37
3-37-2	Molecule Type	DNA
3-37-3	Length	126
3-37-4	Features Location/Qualifiers	<b>source 1..126</b> mol_type=other DNA organism=synthetic construct
3-37-5	NonEnglishQualifier Value Residues	aaacggggca gaaagaaact cctgtatata ttcaaacaac catttatgag accagtacaa 60 actactcaag aggaagatgg ctgtagctgc cgatttccag aagaagaaga aggaggatgt 120 gaactg 126
<b>3-38</b>	<b>Sequences</b>	
3-38-1	Sequence Number [ID]	38
3-38-2	Molecule Type	DNA
3-38-3	Length	339
3-38-4	Features Location/Qualifiers	<b>source 1..339</b> mol_type=other DNA organism=synthetic construct
3-38-5	NonEnglishQualifier Value Residues	agagtgaagt tcagcaggag cgcagacgcc cccgcgtacc agcagggccca gaaccagctc 60 tataacgagc tcaatctagg acgaagagag gagtacgatg ttttggacaa gagacgtggc 120 cgggaccctg agatgggggg aaagccgaga aggaagaacc ctcaggaagg cctgtacaat 180 gaactgcaga aagataagat ggcggaggcc tacagtgaga ttgggatgaa aggcgagcgc 240 cggaggggca aggggcacga tggcctttac cagggctctca gtacagccac caaggacacc 300 tacgacgccc ttcacatgca ggccctgccc cctcgctaa 339
<b>3-39</b>	<b>Sequences</b>	
3-39-1	Sequence Number [ID]	39
3-39-2	Molecule Type	DNA
3-39-3	Length	2250
3-39-4	Features Location/Qualifiers	<b>source 1..2250</b> mol_type=other DNA organism=synthetic construct
3-39-5	NonEnglishQualifier Value Residues	atggccttac cagtgaccgc cttgctctcg ccgctggcct tgcctgctca cgcgccagg 60 ccggaagtgc agctgggtga gtctggggga ggcttggtac agcctggcag gtccctgaga 120 ctctctctg cagcctctgg attcaccttt aatgattatg ccacatgactg ggcccgccaa 180 gctccaggga agggcctgga gtgggtctca actattagtt ggaatagtgg ttccataggg 240 tatgcccact ctgtgaaggg ccgattcacc atctccagag acaacgcca gaagtccctg 300 tatctgcaaa tgaacagtct gagagctgag gacacggcct tgtattactg tgcaaaagat 360 atacagtagc gcaactacta ctacggtagt gacgtctggg gccaaaggac cacggtcacc 420 gtctctctcag gcagtagtag cgggtggggc tcggggggcg gttccgggtg gggcggcagc 480 agcgaaatg tgttgacaca gtctccagcc accctgtact tgcctccagg ggaagagacc 540 accctctctc gcagggccag tcagagtgtt agcagctact tagcctggta ccaacagaaa 600 cctggccagg ctcccaggct cctcatctat gatgcatcca acaggggccac tggcatccca 660 gccagggtca gtggcagtgg gtctgggaca gacttcaact tcaccatcag cagcctagag 720 cctgaagatt ttgcagttta ttactgtcag cagcgtagca actggccgat cacctcggc 780 caagggacac gactggagat taaaggaggt ggtggatccg acatccagat gaccagctcc 840 ccctctctccc tgtccgctc cgtggggcag cgggtgacca tcacctgccc ggcctcccag 900 ggcatctcca actacctgaa ctgggtaccag cagaagcccc gcaaggcccc caagccctg 960 atctactaca cctccaacct gcagtcggc gtgcctccc ggttctccgg ctcccgtctc 1020 ggcaccgact acacctgac catctctctc ctgcagcccc aggactctgc cacctactac 1080 tgcattgggc agaccatctc ctctacacc ttccggccagg gcaccaagct ggagatcaag 1140 ggtggcggtg gctcggggcg tgggtggctg ggtggcggcg gatctgaggt gcagctgggt 1200

		<p>gagtcgcgcg gggcctggt gcagcccggc ggctccctgc ggctgtcctg cgccgcctcc 1260</p> <p>ggcttcacct tctccaact cgacatggcc tgggtgctggc aggcccccg caaggcctg 1320</p> <p>gtgtgggtgt cctccatcac caccggcgcc gaccacgcca tctacgcca ctccgtgaag 1380</p> <p>ggcgggttca ccatctcccg ggacaacgcc aagaacacc tgtactgca gatgaactcc 1440</p> <p>ctgcgggccc aggacacccg cgtgtactac tgcgtgctgc acggctacta cgacggctac 1500</p> <p>cacctgttcg actactgggg ccaggggacc ctgggtgacc tgcctcctt cgtgccggtc 1560</p> <p>ttcctgccag cgaagcccac cagcagcca gcgccgcag caccaacacc ggcgcccacc 1620</p> <p>atcgcgctgc agcccctgtc ctgcgcccga gaggcgtgcc ggccagcggc ggggggcgca 1680</p> <p>gtgcacacga gggggctgga cttgcctgt gatatacaca tctggcgccc cttggcggg 1740</p> <p>acttgtgggg tccttctcct gtcactggtt atcaccctt actgcaaacg gggcagaaag 1800</p> <p>aaactcctgt atataattca acaaccttt atgagaccag tacaactac tcaagaggaa 1860</p> <p>gatggctgta gctgcccatt tccagaagaa gaagaaggag gatgtgaact gagagtgaag 1920</p> <p>ttcagcagga gcgcagacgc ccccgctac cagcagggcc agaaccagct ctataacgag 1980</p> <p>ctcaatctag gacgaagaga ggagtacgat gttttggaca agagacgtgg ccgggaccct 2040</p> <p>gagatggggg gaaagccgag aaggaagaac cctcaggaag gcctgtacaa tgaactgcag 2100</p> <p>aaagataaga tggcggaggc ctacagttag attgggatga aaggcgagcg ccggaggggc 2160</p> <p>aaggggcagc atggccttta ccagggtctc agtacagcca ccaaggacac ctacgacgcc 2220</p> <p>cttcacatgc aggcctgccc cctcgcctaa 2250</p>
3-40	<b>Sequences</b>	
3-40-1	Sequence Number [ID]	40
3-40-2	Molecule Type	AA
3-40-3	Length	749
3-40-4	Features	<b>source 1..749</b>
	Location/Qualifiers	mol_type=protein organism=synthetic construct
	NonEnglishQualifier Value	
3-40-5	Residues	<p>MALPVTALLL PLALLLHAAR PEVQLVESGG GLVQPGRSLR LSCAASGFTF NDYAMHWVRQ 60</p> <p>APGKGLEWVS TISWNSGSIG YADSVKGRFT ISRDNAKKS LYLQMNSLRAE DTALYYCAKD 120</p> <p>IQYGNYYGDM DVWGQTTVT VSSGSTSGGG SGGGSGGGGS SEIVLTQSPA TSLSPGERA 180</p> <p>TLSCRASQSV SSYLAWYQK PGQAPRLLIY DASNRATGIP ARFSGSGSGT DFTLTISSLE 240</p> <p>PEDFAVYCYQ QRSNWPITFG QGTRLEIKGG GGSDIQMTQS PSSLSASVGD RVTITCRASQ 300</p> <p>GISNYLNWYQ QKPGKAPKPL IYYTSLNLSG VPSRFSGSGS GTDYTLTISS LQPEDFATYY 360</p> <p>CMGQTISSYT FGQGTKLEIK GGGGSGGGGS GGGGSEVQLV ESGGGLVQPG GSLRLSCAAS 420</p> <p>GFTFSNFDMA WVRQAPGKGL VWVSSITGA DHAIYADSVK GRFTISRDNA KNTLYLQMNS 480</p> <p>LRAEDTAVY CVRHGYDGY HLFDYWGQGT LVTVSSFVPL FLPKPTTTP APRPPTPAPT 540</p> <p>IASQPLSLRP EACRPAAGGA VHTRGLDFAC DIYIWAPLAG TCGVLLLSLV ITLYCKRGRK 600</p> <p>LLLYIFKQPF MRPVQTTQEE DGCSCRFPEE EGGCELRVK FRSADAPAY QQGQNQLYNE 660</p> <p>LNLGRREEYD VLDKRRGRDP EMGGKPRRKN PQEGLYNELQ KDKMAEAYSE IGMKGERRR 720</p> <p>KGHDGLYQGL STATKDYDA LHMQUALPPR 749</p>
3-41	<b>Sequences</b>	
3-41-1	Sequence Number [ID]	41
3-41-2	Molecule Type	DNA
3-41-3	Length	63
3-41-4	Features	<b>source 1..63</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-41-5	Residues	<p>atggccttac cagtgaccgc cttgctcctg ccgctggcct tgctgctcca cgccgccagg 60</p> <p>ccg 63</p>
3-42	<b>Sequences</b>	
3-42-1	Sequence Number [ID]	42
3-42-2	Molecule Type	DNA
3-42-3	Length	366
3-42-4	Features	<b>source 1..366</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-42-5	Residues	<p>gaagtgcagc tgggtggagtc tgggggaggc ttggtacagc ctggcaggtc cctgagactc 60</p> <p>tcctgtgca cctctggatt cacctttaat gattatgcca tgcactgggt ccgccaagct 120</p> <p>ccagggaaag gcctggagtg ggtctcaact attagttgga atagtggttc cataggtctat 180</p> <p>gcggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa gtccctgtat 240</p> <p>ctgcaaatga acagtctgag agctgaggac acggccttgt attactgtgc aaaagatata 300</p> <p>cagtacggca actactacta cggtatggac gtctggggcc aagggaccac ggtcaccgctc 360</p> <p>tcctca 366</p>
3-43	<b>Sequences</b>	
3-43-1	Sequence Number [ID]	43
3-43-2	Molecule Type	DNA
3-43-3	Length	54
3-43-4	Features	<b>source 1..54</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	

3-43-5	Residues	ggcagtacta gcggtggtgg ctccgggggc ggttccggtg ggggcggcag cagc	54
<b>3-44</b>	<b>Sequences</b>		
3-44-1	Sequence Number [ID]	44	
3-44-2	Molecule Type	DNA	
3-44-3	Length	321	
3-44-4	Features	<b>source 1..321</b>	
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct	
	NonEnglishQualifier Value		
3-44-5	Residues	gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccagggga aagagccacc 60 ctctcctgca gggccagtcg gagtgttagc agctacttag cctggtacca acagaaacct 120 ggccaggctc ccaggctcct catctatgat gcatccaaca gggccactgg catcccagcc 180 aggttcagtg gcagtgggtc tgggacagac ttcactctca ccatcagcag cctagagcct 240 gaagattttg cagtttatta ctgtcagcag cgtagcaact ggccgatcac cttcggccaa 300 gggacacgac tggagattaa a	321
<b>3-45</b>	<b>Sequences</b>		
3-45-1	Sequence Number [ID]	45	
3-45-2	Molecule Type	DNA	
3-45-3	Length	15	
3-45-4	Features	<b>source 1..15</b>	
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct	
	NonEnglishQualifier Value		
3-45-5	Residues	ggaggtggtg gatcc	15
<b>3-46</b>	<b>Sequences</b>		
3-46-1	Sequence Number [ID]	46	
3-46-2	Molecule Type	DNA	
3-46-3	Length	363	
3-46-4	Features	<b>source 1..363</b>	
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct	
	NonEnglishQualifier Value		
3-46-5	Residues	gaggtgcagc tgggtggagtc cggcgggcgc ctggtgcagc ccggcggtc cctgcggctg 60 tcttgccgcc cctccggtt caccttctcc aacttcgaca tggcctgggt gcggcaggcc 120 cccggcaagg gcctggtgtg ggtgtcctcc atcaccaccg gcgccacca cgccatctac 180 gccgactccg tgaagggccg gttcaccatc tcccgggaca acgccaagaa caccctgtac 240 ctgcagatga actccctcgg gggcgaggac accgcccgtg actactgcgt gcggcacggc 300 tactacgacg gctaccacct gttcgactac tggggccagg gcacctggt gacctgtgcc 360 tcc	363
<b>3-47</b>	<b>Sequences</b>		
3-47-1	Sequence Number [ID]	47	
3-47-2	Molecule Type	DNA	
3-47-3	Length	45	
3-47-4	Features	<b>source 1..45</b>	
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct	
	NonEnglishQualifier Value		
3-47-5	Residues	ggtggcggtg gctcgggcgg tgggtgggtcg ggtggcgcg gatct	45
<b>3-48</b>	<b>Sequences</b>		
3-48-1	Sequence Number [ID]	48	
3-48-2	Molecule Type	DNA	
3-48-3	Length	321	
3-48-4	Features	<b>source 1..321</b>	
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct	
	NonEnglishQualifier Value		
3-48-5	Residues	gacatccaga tgaccagtc ccctcctcc ctgtccgct ccgtgggcga ccgggtgacc 60 atcacctgcc gggcctcca gggcatctcc aactacctga actggtacca gcagaagccc 120 ggcaaggccc ccaagccct gatctactac acctccaacc tgcagtccgg cgtgcctcc 180 cggttctccg gctccggtc cggcaccgac tacacctga ccatctctc cctgcagccc 240 gaggacttcg ccactacta ctgcatgggc cagaccatct cctcctacac cttcggccag 300 ggcaccaagc tggagatcaa g	321
<b>3-49</b>	<b>Sequences</b>		
3-49-1	Sequence Number [ID]	49	
3-49-2	Molecule Type	DNA	
3-49-3	Length	165	
3-49-4	Features	<b>source 1..165</b>	
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct	
	NonEnglishQualifier Value		

3-49-5	Residues	ttcgtgcccg tcttctgcc agcgaagccc accacgacgc cagcgcccgcg accaccaaca 60 ccggcgccca ccacgcgctc gcagcccctg tccctgcgcc cagaggcgtg ccggccacgcg 120 gcggggggcg cagtgcacac gagggggctg gacttcgctt gtgat 165
<b>3-50</b>	<b>Sequences</b>	
3-50-1	Sequence Number [ID]	50
3-50-2	Molecule Type	DNA
3-50-3	Length	72
3-50-4	Features	<b>source 1..72</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-50-5	Residues	atctacatct gggcgccctt ggcgggact tgtgggtcc ttctctgtc actggttacc 60 accctttact gc 72
<b>3-51</b>	<b>Sequences</b>	
3-51-1	Sequence Number [ID]	51
3-51-2	Molecule Type	DNA
3-51-3	Length	126
3-51-4	Features	<b>source 1..126</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-51-5	Residues	aaacggggca gaaagaaact cctgtatata ttcaaacaac catttatgag accagtacaa 60 actactcaag aggaagatgg ctgtagctgc cgatttccag aagaagaaga aggaggatgt 120 gaactg 126
<b>3-52</b>	<b>Sequences</b>	
3-52-1	Sequence Number [ID]	52
3-52-2	Molecule Type	DNA
3-52-3	Length	339
3-52-4	Features	<b>source 1..339</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-52-5	Residues	agagtgaagt tcagcaggag cgcagacgcc cccgcgtacc agcagggcca gaaccagctc 60 tataacgagc tcaatctagg acgaagagag gactacgatg ttttgacaa gagacgtggc 120 cgggaccctg agatgggggg aaagccgaga aggaagaacc ctcaggaagg cctgtacaat 180 gaactgcaga aagataagat ggcggaggcc tacagtgaga ttgggatgaa aggcgagcgc 240 cggaggggca aggggcacga tggcctttac cagggctca gtacagccac caaggacacc 300 tacgacgccc ttcacatgca ggcctcgccc cctcgctaa 339
<b>3-53</b>	<b>Sequences</b>	
3-53-1	Sequence Number [ID]	53
3-53-2	Molecule Type	DNA
3-53-3	Length	2250
3-53-4	Features	<b>source 1..2250</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-53-5	Residues	atggccttac cagtgaccgc cttgctctcg ccgctggcct tgcctgcca cgcgccagg 60 ccggaagtgc agctggtgga gtctggggga ggcttggtac agcctggcag gtcctgaga 120 ctctctctg cagcctctgg attcaccttt aatgattatg ccatgcactg ggtccggcaa 180 gctccaggga aggccttga gtgggtctca actattagtt ggaatagtgg ttccataggc 240 tatgcggact ctgtgaaggg ccgattcacc atctccagag acaacgcca gaagtccctg 300 tatctgcaaa tgaacagtct gagagctgag gacacggcct tgtattactg tgcaaaagat 360 atacagtacg gcaactacta ctacggtagt gaogtctggg gccaaaggac cacggtcacc 420 gtctctcag gcagtagtag cggtggtggc tccgggggag gttccggtag gggcggcagc 480 agcgaaattg tgttgacaca gtctccagcc accctgtctt tgtctccagg ggaagagacc 540 accctctcct gcagggccag tcagagtgtt agcagctact tagcctggta ccaacagaaa 600 cctggccagg ctcccaggct cctcatctat gatgcatcca acagggcca tggcatocca 660 gccaggttca gtggcagtgg gtctgggaca gacttcaact tcaacctcag cagcctagag 720 cctgaagatt ttgcagtta ttaactgtcag cagcgtagca actggccgat cacctcggc 780 caagggacac gactggagat taaaggagg gtggatccg aggtgcagct ggtggagtcc 840 ggcggcggcc tggtgacgcc cggcggctcc ctgcccgtgt cctgcccgcg ctcccgttc 900 accttctcca acttcgacat ggcctgggtg cggcaggccc ccggcaaggg cctggtgtgg 960 gtgtctcca tcaccaccgg cgcgcgacc gccatctacg ccgactccgt gaagggccgg 1020 ttcaccatct cccgggaca cccaagaac accctgtacc tgcagatgaa ctcccgcgg 1080 gccagggaca ccgcccgtga ctactcgtg cggcacggct actacgacgg ctaccaccgt 1140 ttcgactact ggggccaggg caccctgggt accgtgtcct ccggtggcgg tggctcgggc 1200 ggtggtgggt cgggtggcgg cggatctgac atccagatga cccagtcacc ctccctcctg 1260 tccgctccg tggcgaccg ggtgaccatc acctgcccgg cctcccaggg catctccaac 1320 tacctgaact ggtaccagca gaagcccggc aaggccccc agcccctgat ctactacacc 1380 tccaacctgc agtccggcgt gccctcccgg ttctccggct ccggtccgg caccgactac 1440 accctgacca tctctcctc gaagcccag gacttcgcca cctactactg catgggccag 1500 accatctcct cctacacctt cggccagggc accaagctgg agatcaagtt cgtgcccggc 1560

		<p>ttcctgccag cgaagccac caccgaccca gcgcgcgcac caccaacacc ggcgcccacc 1620  atcgcgtcgc agcccctgtc cctgcccaca gaggcgtgcc ggccagcggc gggggcgca 1680  gtgcacacga ggggctgga cttgcctgt gatattctaca tctggcgcc cttggccggg 1740  acttggggg tccttctct gtcactggtt atcacccttt actgcaaacg gggcagaaa 1800  aaactcctgt atatatcaa acaaccattt atgagaccag tacaactac tcaagaggaa 1860  gatggctgta gctgccgatt tccagaagaa gaagaaggag gatgtgaact gagagtgaag 1920  ttcagcagga gcgcagacgc ccccgcgtac cagcagggcc agaaccagct ctataacgag 1980  ctcaatctag gacgaagaga ggagtagat gttttggaca agagacgtgg ccgggaccct 2040  gagatggggg gaaagccgag aaggaagaac cctcaggaag gcctgtacaa tgaactgcag 2100  aaagataaga tggcggaggc ctacagttag attgggatga aaggcgagcg ccggaggggc 2160  aaggggcacg atggccttta ccagggtctc agtacagcca ccaaggacac ctacgacgcc 2220  cttcacatgc aggcctgcc cctcgcctaa 2250</p>
3-54	<b>Sequences</b>	
3-54-1	Sequence Number [ID]	54
3-54-2	Molecule Type	AA
3-54-3	Length	749
3-54-4	Features	<b>source 1..749</b>
	Location/Qualifiers	mol_type=protein organism=synthetic construct
	NonEnglishQualifier Value	
3-54-5	Residues	<p>MALPVTALLL PLALLLHAAR PEVQLVESGG GLVQPGRSLR LSCAASGFTF NDYAMHWVRQ 60  APGKGLEWVS TISWNSGSIG YADSVKGRFT ISRDNAKKS LYLQMNSLRAE DTALYCAKD 120  IQYGNYYGDM DVWGQGTTVT VSSGSTSGGG SGGSGGGGS SEIVLTQSPA TSLSPGERA 180  TLSCRASQSV SSYLAWYQK PQQAPRLLIY DASNRAIGIP ARFSGSGSGT DFTLTISSE 240  PEDFAVYYCQ QRSNWPITFG QGTRLEIKGG GGSEVQLVES GGGLVQPQGS LRLSCAASGF 300  TFSNFDMAWV RQAPGKGLVW VSSITGADH AIYADSVKGR FTISRDNKN TLYLQMNSLR 360  AEDTAVYYCV RHGYDGYHL FDYWGQTLV TVSSGGGSG GGGSGGGSD IQMTQSPSSL 420  SASVGDRTVI TCRASQGISN YLNWYQQKPG KAPKPLIYYT SNLQSGVPSR FSGSGSGTDY 480  TLTISLQPE DFATYYCMGQ TISSYTFGQG TKLEIKFVPV FLPKPTTTP APRPPTPAPT 540  IASQPLSLRP EACRPAAGGA VHTRGLDFAC DIYIWAPLAG TCGVLLLSLV ITLYCKRGRK 600  KLLYIFKQPF MRPVQTTQEE DGCSCRFP EE EGGCELRVK FRSADAPAY QQGQNLQYNE 660  LNLGRREEYD VLDKRRGRDP EMGGKPRRKN PQEGLYNELQ KDKMAEAYSE IGMKGERRR 720  KGDGLYQGL STATKDTYDA LHMQLPPR 749</p>
3-55	<b>Sequences</b>	
3-55-1	Sequence Number [ID]	55
3-55-2	Molecule Type	DNA
3-55-3	Length	63
3-55-4	Features	<b>source 1..63</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-55-5	Residues	<p>atggccttac cagtgaccgc cttgctcctg ccgctggcct tgctgctcca cgccgccagg 60  ccg 63</p>
3-56	<b>Sequences</b>	
3-56-1	Sequence Number [ID]	56
3-56-2	Molecule Type	DNA
3-56-3	Length	321
3-56-4	Features	<b>source 1..321</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-56-5	Residues	<p>gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccagggga aagagccacc 60  ctctcctgca gggccagtc gagtgtagc agctacttag cctggtacca acagaaacct 120  ggccaggctc ccaggctcct catctatgat gcatccaaca gggccactgg catcccagcc 180  aggttcagtg gcagtgggtc tgggacagac ttoactctca ccatcagcag cctagagcct 240  gaagattttg cagtttatta ctgtcagcag cgtagcaact ggccgatcac cttcggccaa 300  gggacacgac tggagattaa a 321</p>
3-57	<b>Sequences</b>	
3-57-1	Sequence Number [ID]	57
3-57-2	Molecule Type	DNA
3-57-3	Length	54
3-57-4	Features	<b>source 1..54</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-57-5	Residues	<p>ggcagtacta gcggtggtgg ctccgggggc ggttccggtg gggcgccag cagc 54</p>
3-58	<b>Sequences</b>	
3-58-1	Sequence Number [ID]	58
3-58-2	Molecule Type	DNA
3-58-3	Length	366
3-58-4	Features	<b>source 1..366</b>

3-58-5	Location/Qualifiers NonEnglishQualifier Value Residues	mol_type=other DNA organism=synthetic construct  gaagtgcagc tggtaggagtc tgggggaggc ttggtacagc ctggcaggtc cctgagactc 60 tcctgtgcag cctctggatt cacctttaat gattatgcca tgcactgggt cgggcaagct 120 ccagggaagg gcctggagtg ggtctcaact attagttgga atagtgttcc cataggttat 180 gcgactctg tgaagggccg atccaccatc tccagagaca acgccaagaa gtcctctgtat 240 ctgcaaatga acagtctgag agctgaggac acggccttgt attactgtgc aaaagatata 300 cagtacggca actactacta cggtatggac gtctgtgggc aagggaccac ggtcacctgc 360 tcctca 366
<b>3-59</b> 3-59-1 3-59-2 3-59-3 3-59-4 3-59-5	<b>Sequences</b> Sequence Number [ID] Molecule Type Length Features Location/Qualifiers NonEnglishQualifier Value Residues	59 DNA 15 <b>source 1..15</b> mol_type=other DNA organism=synthetic construct  ggagggtggtg gatcc 15
<b>3-60</b> 3-60-1 3-60-2 3-60-3 3-60-4 3-60-5	<b>Sequences</b> Sequence Number [ID] Molecule Type Length Features Location/Qualifiers NonEnglishQualifier Value Residues	60 DNA 363 <b>source 1..363</b> mol_type=other DNA organism=synthetic construct  gaggtgcagc tggtaggagtc cggcgggcgc ctggtgcagc ccggcggtc cctgcggtc 60 tcctgcgcgc cctccggtt caccttctcc aacttcgaca tggcctgggt gcggcaggcc 120 cccggcaagg gcctgggtg ggtgtctctc atcaccaccg gcgcccacca cgccatctac 180 gccgactccg tgaagggccg gttcaccatc tcccgggaca acgccaagaa caccctgtac 240 ctgcagatga actccctgcg ggcgaggac accgcccgtg actactgcgt gcggcacggc 300 tactacgacg gctaccacct gttcgactac tggggccagg gcacctgggt gacctgtgcc 360 tcc 363
<b>3-61</b> 3-61-1 3-61-2 3-61-3 3-61-4 3-61-5	<b>Sequences</b> Sequence Number [ID] Molecule Type Length Features Location/Qualifiers NonEnglishQualifier Value Residues	61 DNA 45 <b>source 1..45</b> mol_type=other DNA organism=synthetic construct  ggtggcggtg gctcgggcgg tggtaggagtc ggtggcggcg gatct 45
<b>3-62</b> 3-62-1 3-62-2 3-62-3 3-62-4 3-62-5	<b>Sequences</b> Sequence Number [ID] Molecule Type Length Features Location/Qualifiers NonEnglishQualifier Value Residues	62 DNA 321 <b>source 1..321</b> mol_type=other DNA organism=synthetic construct  gacatccaga tgaccagtc cccctctctc ctgtccgct ccgtggggcga ccgggtgacc 60 atcacctgcc gggcctcca gggcatctcc aactacctga actggtacca gcagaagccc 120 ggcaaggccc ccaagcccct gatctactac acctccaacc tgcagtccgg cgtgccctcc 180 cggttctccg gctccggctc cggcaccgac tacacctga ccatctctc cctgcagccc 240 gaggacttcg ccactacta ctgcatgggc cagaccatct cctcctacac cttcggccag 300 ggcaccaagc tggagatcaa g 321
<b>3-63</b> 3-63-1 3-63-2 3-63-3 3-63-4 3-63-5	<b>Sequences</b> Sequence Number [ID] Molecule Type Length Features Location/Qualifiers NonEnglishQualifier Value Residues	63 DNA 165 <b>source 1..165</b> mol_type=other DNA organism=synthetic construct  ttcgtgccgg tcttctctcc agcgaagccc accacgacgc cagcgcgcgc accaccaaca 60 ccggcgccca ccctcgcgc gcagcccctg tccctgcgcc cagaggcgtg ccggccagcg 120 gcggggggcg cagtgcacac gagggggctg gacttcgct gtgat 165
<b>3-64</b> 3-64-1	<b>Sequences</b> Sequence Number [ID]	64

3-64-2	Molecule Type	DNA
3-64-3	Length	72
3-64-4	Features	<b>source 1..72</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
3-64-5	NonEnglishQualifier Value Residues	atctacatct gggcgccctt ggccgggact tgtggggctc ttctcctgtc actggttacc 60 accctttact gc 72
<b>3-65</b>	<b>Sequences</b>	
3-65-1	Sequence Number [ID]	65
3-65-2	Molecule Type	DNA
3-65-3	Length	126
3-65-4	Features	<b>source 1..126</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
3-65-5	NonEnglishQualifier Value Residues	aaacggggca gaaagaaact cctgtatata ttcaaacaac catttatgag accagtacaa 60 actactcaag aggaagatgg ctgtagctgc cgatttccag aagaagaaga aggagatgt 120 gaactg 126
<b>3-66</b>	<b>Sequences</b>	
3-66-1	Sequence Number [ID]	66
3-66-2	Molecule Type	DNA
3-66-3	Length	339
3-66-4	Features	<b>source 1..339</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
3-66-5	NonEnglishQualifier Value Residues	agagtgaagt tcagcaggag cgcagacgcc cccgcgtacc agcagggcca gaaccagctc 60 tataacgagc tcaatctagg acgaagagag gactacgatg ttttggacaa gagacgtggc 120 cgggaccctg agatgggggg aaagccgaga aggaagaacc ctcaggaagg cctgtacaat 180 gaactgcaga aagataagat ggcggaggcc tacagtgaga ttgggatgaa aggcgagcgc 240 cggaggggca aggggcacga tggcctttac cagggtctca gtacagccac caaggacacc 300 tacgacgccc ttcacatgca ggccttgccc cctcgctaa 339
<b>3-67</b>	<b>Sequences</b>	
3-67-1	Sequence Number [ID]	67
3-67-2	Molecule Type	DNA
3-67-3	Length	2250
3-67-4	Features	<b>source 1..2250</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
3-67-5	NonEnglishQualifier Value Residues	atggccttac cagtgaccgc ctgtctctcg ccgctggcct tgetgtccca cgccgccagg 60 cggaaattg tgttgacaca gtctccagcc accctgtcct tgtctccagg ggaaagagcc 120 accctctcct gcagggccag tcagagtgtt agcagctact tagcctggta ccaacagaaa 180 cctggccagg ctcccaggct cctcatctat gatgcatcca acagggccac tggcatccca 240 gccaggttca gtggcagtgg gtctgggaca gacttcaactc tcaccatcag cagcctagag 300 cctgaagatt ttgcagtta ttaactgtcag cagcgtagca actggccgat caccttcggc 360 caagggacac gactggagat taaaggcagt actagcgtg gtggctccgg gggcggttcc 420 ggtgggggcg gcagcagcga agtgacgctg gtggagtctg ggggaggctt ggtacagcct 480 ggcagggtccc tgagactctc ctgtgcagcc tctggattca cctttaatga ttatgccatg 540 cactgggtcc ggcaagctcc agggaagggc ctggagtggg tctcaactat tagttggaat 600 agtggttcca taggctatgc ggactctgtg aagggccgat tcaccatctc cagagacaac 660 gccaagaagt ccctgtatct gcaaatgaac agtctgagag ctgaggacac ggccttgtat 720 tactgtgcaa aagatataca gtacggcaac tactactacg gtatggacgt ctggggccaa 780 gggaccacgg tcaccgtctc ctcaggaggt ggtggatccg aggtgcagct ggtggagtcc 840 ggcggcggcc tggtgacgcc cggcggctcc ctgcccgtgt cctgcccgcg ctcccgttc 900 accttctcca acttcgacat ggcctgggtg cggcaggccc ccggcaaggg cctggtgtgg 960 gtgtctccca tcaccaccgg cgccgaccac gccatctacg ccgactccgt gaagggccgg 1020 ttaccatct cccgggacaa cgccaagaac accctgtacc tgcagatgaa ctccctgagg 1080 gccgaggaca ccgccgtgta ctactgcgtg cggcacggct actacgacgg ctaccacctg 1140 ttcgactact ggggccaggg caccctgggt accgtgtcct ccggtggcgg tggtcggggc 1200 ggtgggtggg cgggtggcgg cggatctgac atccagatga cccagctccc ctccctcctg 1260 tccgctccg tggcgaccc ggtagccatc acctgcccgg cctcccagg catctccaac 1320 tacctgaact ggtaccagca gaagcccggc aaggccccca agcccctgat ctactacacc 1380 tccaacctgc agtccggcgt gccctcccgg ttctccggct ccggtcccgg caccgactac 1440 accctgacca tctcctcct gcagcccagg gacttcgcca cctactactg catgggccag 1500 accatctcct cctacacctt cggccagggc accaagctgg agatcaagtt cgtgcccggc 1560 ttcctgccag cgaagcccac cacgacgcca gcgccgcgac caccaacacc ggcgcccacc 1620 atcgcgctcg agcccctgtc cctgcgcccc gaggcgtgccc ggcagccggc gggggccgca 1680 gtgcacacga ggggctgga cttcgctgt gatattctaca tctggcgccc cttggccggg 1740 acttgtgggg tccttctcct gtcactgggt atcacccttt actgcaaacg gggcagaaa 1800 aaactcctgt atatattcaa acaaccattt atgagaccag taaaaactac tcaagaggaa 1860

		gatggctgta gctgccgatt tccagaagaa gaagaaggag gatgtgaact gagagtgaag 1920 ttcagcagga gcgcagacgc ccccgcgtac cagcaggggc agaaccagct ctataacgag 1980 ctcaatctag gacgaagaga ggagtacgat gttttggaca agagacgtgg cggggaccct 2040 gagatggggg gaaagccgag aaggaagaac cctcaggaag gcctgtacaa tgaactgcag 2100 aaagataaga tggcggaggc ctacagttag attgggatga aaggcgagcg ccggaggggc 2160 aaggggcacg atggccttta ccagggtctc agtacagcca ccaaggacac ctacgacgcc 2220 cttcacatgc aggcctgccc cctcgcctaa 2250
<b>3-68</b>	<b>Sequences</b>	
3-68-1	Sequence Number [ID]	68
3-68-2	Molecule Type	AA
3-68-3	Length	749
3-68-4	Features	<b>source 1..749</b>
	Location/Qualifiers	mol_type=protein organism=synthetic construct
	NonEnglishQualifier Value	
3-68-5	Residues	MALPVTALLL PLALLLHAAR PEIVLTQSPA TLSLSPGERA TLSCRASQSV SSYLAWYQQK 60 PGQAPRLLIY DASNRATGIP ARFSGSGSGT DFTLTISLE PEDFAVYQC QRSNWPITFG 120 QGTRLEIKGS TSGGSGSGGS GGGGSSEVQL VESGGGLVQP GRSLRLSCAA SGFTFNDYAM 180 HWVRQAPGKG LEWVSTISWN SGSIGYADSV KGRFTISRDN AKKSLYLQMN SLRAEDTALY 240 YCAKDIQYGN YYGMDVWVQ GTVTVVSSGG GGSEVQLVES GGLVQPGGS LRLSCAASGF 300 TFSNFDMAVW RQAPGKGLVW VSSITTGADH AIYADSVKGR FTISRDNAKN TLYLQMNLSR 360 AEDTAVYYCV RHGYDGYHL FDYWGQGLV TVSSGGGSG GGGSGGGSD IQMTQSPSSL 420 SASVGRVTI TCRASQGISN YLNWYQKPG KAPKPLIYTT SNLQSGVPSR FSGSGSGTDY 480 TLTISLQPE DFATYYCMGQ TISSYTFGQG TKLEIKFVVP FLPKPTTTP APRPPTPAPT 540 IASQPLSLRP EACRPAAGGA VHTRGLDFAC DIYIWAPLAG TCGVLLLSLV ITLYCKRGRK 600 KLLYIFKQPF MRPVQTTQEE DGCSCRFPPE EGGCELRVK FRSADAPAY QGQNLQLYNE 660 LNLGRREEYD VLDKRRGRDP EMGGKPRRKN PQEGLYNELQ KDKMAEAYSE IGMKGERRRG 720 KGHDGLYQGL STATKDTYDA LHMQUALPPR 749
<b>3-69</b>	<b>Sequences</b>	
3-69-1	Sequence Number [ID]	69
3-69-2	Molecule Type	DNA
3-69-3	Length	63
3-69-4	Features	<b>source 1..63</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-69-5	Residues	atggccttac cagtgaccgc ctgtctctcg ccgctggcct tgctgctcca cgccgccagg 60 ccg 63
<b>3-70</b>	<b>Sequences</b>	
3-70-1	Sequence Number [ID]	70
3-70-2	Molecule Type	DNA
3-70-3	Length	321
3-70-4	Features	<b>source 1..321</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-70-5	Residues	gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccagggga aagagccacc 60 ctctoctgca gggccagtc gagtgtagc agctacttag cctggtacca acagaacct 120 ggccaggctc ccaggctcct catctatgat gcatccaaca gggccactgg catccagcc 180 aggttcagtg gcagtgggto tgggacagac ttcactctca ccatcagcag cctagagcct 240 gaagattttg cagtttatta ctgtcagcag cgtagcaact ggccgatcac cttcggccaa 300 gggacacgac tggagattaa a 321
<b>3-71</b>	<b>Sequences</b>	
3-71-1	Sequence Number [ID]	71
3-71-2	Molecule Type	DNA
3-71-3	Length	54
3-71-4	Features	<b>source 1..54</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-71-5	Residues	ggcagtaact gcggtggtgg ctccgggggc ggttccggtg ggggcggcag cagc 54
<b>3-72</b>	<b>Sequences</b>	
3-72-1	Sequence Number [ID]	72
3-72-2	Molecule Type	DNA
3-72-3	Length	366
3-72-4	Features	<b>source 1..366</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-72-5	Residues	gaagtgcagc tgggtggagtc tggggaggc ttggtacagc ctggcaggtc cctgagactc 60 tcctgtgcag cctctggatt caccttaaat gattatgcca tgcactgggt ccggcaagct 120

		ccaggggaagg gctctggagtg ggtctcaact attagttgga atagtggttc cataggtat 180 gcggaactctg tgaagggccg attcaccatc tccagagaca acgccaagaa gtcctgtat 240 ctgcaaatga acagtctgag agctgaggac acggccttgt attactgtgc aaaagatata 300 cagtacggca actactacta cggataggac gtctggggcc aagggaccac ggtcaccgtc 360 tcctca 366	
<b>3-73</b>	<b>Sequences</b>		
3-73-1	Sequence Number [ID]	73	
3-73-2	Molecule Type	DNA	
3-73-3	Length	15	
3-73-4	Features	<b>source 1..15</b>	
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct	
	NonEnglishQualifier Value		
3-73-5	Residues	ggaggtggtg gatcc	15
<b>3-74</b>	<b>Sequences</b>		
3-74-1	Sequence Number [ID]	74	
3-74-2	Molecule Type	DNA	
3-74-3	Length	363	
3-74-4	Features	<b>source 1..363</b>	
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct	
	NonEnglishQualifier Value		
3-74-5	Residues	gaggtgcagc tggtaggtc cggcggcggc ctggtgcagc ccggcggtc cctgcggctg 60 tctgcgcgcg cctccggctt caccttctcc aacttcgaca tggcctgggt gcggcaggcc 120 cccggcaagg gctggtgtg ggtgtcctcc atcaccaccg gcgcccacca cgccatctac 180 gccgactccg tgaagggccg gtcaccatc tcccgggaca acgccaagaa caccctgtac 240 ctgcagatga actccctgcg ggccgaggac accgccgtgt actactgctg gcggcacggc 300 tactacgacg gctaccacct gttcgactac tggggccagg gcaccctggt gaccgtgtcc 360 tcc 363	
<b>3-75</b>	<b>Sequences</b>		
3-75-1	Sequence Number [ID]	75	
3-75-2	Molecule Type	DNA	
3-75-3	Length	45	
3-75-4	Features	<b>source 1..45</b>	
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct	
	NonEnglishQualifier Value		
3-75-5	Residues	ggtggcggtg gctcgggcgg tggtaggtcg ggtggcggcg gatct	45
<b>3-76</b>	<b>Sequences</b>		
3-76-1	Sequence Number [ID]	76	
3-76-2	Molecule Type	DNA	
3-76-3	Length	321	
3-76-4	Features	<b>source 1..321</b>	
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct	
	NonEnglishQualifier Value		
3-76-5	Residues	gacatccaga tgaccagtc cccctcctcc ctgtccgct ccgtgggcca ccgggtgacc 60 atcacctgcc gggcctcca gggcatctcc aactactga actggtacca gcagaagccc 120 ggcaaggccc ccaagccctt gatctactac acctccaacc tgcagtccgg cgtgcctcc 180 cggttctccg gctccggctc cggcaccgac tacacctga ccatctctc cctgcagccc 240 gaggacttcg ccaactacta ctgcatgggc cagaccatct cctcctacac ctctggccag 300 ggcaccaagc tggagatcaa g 321	
<b>3-77</b>	<b>Sequences</b>		
3-77-1	Sequence Number [ID]	77	
3-77-2	Molecule Type	DNA	
3-77-3	Length	36	
3-77-4	Features	<b>source 1..36</b>	
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct	
	NonEnglishQualifier Value		
3-77-5	Residues	gagagcaagt acggaccgcc ctgccccctt tgccct	36
<b>3-78</b>	<b>Sequences</b>		
3-78-1	Sequence Number [ID]	78	
3-78-2	Molecule Type	AA	
3-78-3	Length	12	
3-78-4	Features	<b>source 1..12</b>	
	Location/Qualifiers	mol_type=protein organism=synthetic construct	
	NonEnglishQualifier Value		
3-78-5	Residues	ESKYGPCCPP CP	12

<b>3-79</b>	<b>Sequences</b>	
3-79-1	Sequence Number [ID]	79
3-79-2	Molecule Type	DNA
3-79-3	Length	84
3-79-4	Features	<b>source 1..84</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-79-5	Residues	atgttctggg tgctggtggt ggtcggaggc gtgctggcct gctacagcct gctggtcacc 60 gtggccttca tcactctttg ggtg 84
<b>3-80</b>	<b>Sequences</b>	
3-80-1	Sequence Number [ID]	80
3-80-2	Molecule Type	AA
3-80-3	Length	28
3-80-4	Features	<b>source 1..28</b>
	Location/Qualifiers	mol_type=protein organism=synthetic construct
	NonEnglishQualifier Value	
3-80-5	Residues	MFWVLVVVG VLACYSLLVV VAFIIFWV 28
<b>3-81</b>	<b>Sequences</b>	
3-81-1	Sequence Number [ID]	81
3-81-2	Molecule Type	DNA
3-81-3	Length	126
3-81-4	Features	<b>source 1..126</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-81-5	Residues	aaacggggca gaaagaaact cctgtatata ttcaaacaac catttatgag accagtacaa 60 actactcaag aggaagatgg ctgtagctgc cgatttccag aagaagaaga aggagatgt 120 gaactg 126
<b>3-82</b>	<b>Sequences</b>	
3-82-1	Sequence Number [ID]	82
3-82-2	Molecule Type	DNA
3-82-3	Length	336
3-82-4	Features	<b>source 1..336</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-82-5	Residues	cgggtgaagt tcagcagaag cgcgacgcc cctgcctacc agcagggcca gaatcagctg 60 tacaacgagc tgaacctggg cagaagggaa gactacgacg tctctggataa gcgagagaggc 120 cgggaccctg agatgggagg caagcctcgg cggaagaacc cccaggaagg cctgtataac 180 gaactgcaga aagacaagat ggccgagggc tacagcgaga tcggcatgaa gggcgagcgg 240 aggcggggca agggccacga cggcctgtat cagggcctgt ccaccgccac caaggatacc 300 tacgacgccc tgacatgca ggccctgccc ccaagg 336
<b>3-83</b>	<b>Sequences</b>	
3-83-1	Sequence Number [ID]	83
3-83-2	Molecule Type	DNA
3-83-3	Length	2133
3-83-4	Features	<b>source 1..2133</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-83-5	Residues	atggccttac cagtgaccgc cttgctcctg ccgctggcct tgctgctcca cgccgccagg 60 ccgaaattg tgttgacaca gtctccagcc accctgtcct tgtctccagg ggaaagagcc 120 accctctcct gcagggccag tcagagtgtt agcagctact tagcctggta ccaacagaaa 180 cctggccagg ctcccaggct cctcatctat gatgcatcca acagggccac tggcatocca 240 gccaggttca gtggcagtgg gtctgggaca gacttcaact tcaccatcag cagcctagag 300 cctgaagatt ttgcagttta ttactgtcag cagcgtagca actggccgat caccttcggc 360 caagggacac gactggagat taaaggcagt actagcgggt gtggctccgg gggcggttcc 420 ggtggggggc gcagcagcga agtgacagctg gtggagctg ggggaggcct ggtacagcct 480 ggcaggtccc tgagactctc ctgtgcagcc tctggattca cctttaatga ttatgccatg 540 cactgggtcc ggcaagctcc agggaaaggc ctggagtggt tctcaactat tagttggaat 600 agtggttcca taggctatgc ggactctgtg aagggccgat tcaccatctc cagagacaac 660 gccaagaagt cctgtatct gcaaatgaac agtctgagag ctgaggacac ggccttgtat 720 tactgtgcaa aagatataca gtacggcaac tactactacg gtatggacgt ctggggccaa 780 gggaccacgg tcaccgtctc ctcaggaggt ggtggatccg aggtgcagct ggtggagtcc 840 ggcggcggcc tggtgacgcc cggcggctcc ctgcccgtgt cctgcccgcg ctcccgtctc 900 accttctcca acttcgacat ggcctgggtg cggcaggccc ccggcaaggg cctggtgtgg 960 gtgtcctcca tcaccaccgg cgccgaccac gccatctacg ccgactccgt gaagggccgg 1020 ttcaccatct ccggggacaa cgccaagaac accctgtacc tgcagatgaa ctccctgcgg 1080 gccgaggaca ccgccgtgta ctactgcgtg cggcacggct actacgacgg ctaccacctg 1140

		<pre> ttcgactact ggggccaggg caccctgggtg accgtgtcct ccggtggcgg tggctcgggc 1200 ggtaggtgggt cgggtggcgg cggatctgac atccagatga cccagtcccc ctcctccctg 1260 tccgctcccg tgggagaccg ggtgaccatc acctgccggg cctcccaggg catctccaac 1320 tacctgaact ggtaccagca gaagcccggc aaggccccc agccctgat ctactacacc 1380 tccaacctgc agtccggcgt gcctcccgg ttctccggct ccggctccgg caccgactac 1440 accctgacca tctcctcctt cgagcccggg gacttcgcca cctactactg catgggccag 1500 accatctcct cctacacctt cggccaggcg accaagctgg agatcaagga gagcaagta 1560 ggaccgccct gccccccttg cctatgttc tgggtgctgg tgggtgctgg aggcgtgctg 1620 gcctgctaca gcctgctggt caccgtggcc ttcattcatct tttgggtgaa acggggcaga 1680 aagaaactcc tgtatatatt caaacaacca tttatgagac cagtacaaac tactcaagag 1740 gaagatggct gtagctgccc atttccagaa gaagaagaag gaggatgtga actgcggggtg 1800 aagttcagca gaagcgcca gcctccctgcc taccagcagg gccagaaatca gctgtacaac 1860 gagctgaacc tgggcagaag ggaagagtac gacgtcctgg ataagcggag aggcggggag 1920 cctgagatgg gcggcaagcc tcggcggaag aacccccagg aaggcctgta taacgaactg 1980 cagaaagaca agatggcca gcctacagc gagatcggca tgaagggcga gcggagggcg 2040 ggcaagggcc acgacggcct gtatcagggc ctgtccaccg ccaccaagga tacctacgac 2100 gcctgcaca tgcaggccct gcccccaagg taa 2133 </pre>
3-84	<b>Sequences</b>	
3-84-1	Sequence Number [ID]	84
3-84-2	Molecule Type	AA
3-84-3	Length	710
3-84-4	Features	<b>source 1..710</b>
	Location/Qualifiers	mol_type=protein organism=synthetic construct
	NonEnglishQualifier Value	
3-84-5	Residues	<pre> MALPVTALLL PLALLLHAAR PEIVLTQSPA TLSLSPGERA TLSCRASQSV SSYLAWYQQK 60 PGQAPRLLIY DASNRATGIP ARFSGSGSGT DFTLTISSLE PEDFAVYQC QRSNWPITFG 120 QGRLEIKGS TSGGSGGGS GGGGSSEVQL VESGGGLVQP GRSLRLSCAA SGFTFNDYAM 180 HWVRQAPGKG LEWVSTISWN SGSIGYADSV KGRFTISRDN AKKSLYLQMN SLRAEDTALY 240 YCAKDIQYGN YYGMDVWQ GTTVTVSSGG GGSEVQLVES GGLVQPFGS LRLSCAASGF 300 TFSNFDMAWV RQAPGKGLVW VSSITTGADH AIYADSVKGR FTISRDNAKN TLYLQMNCLR 360 AEDTAVYVCV RHGYDGYHL FDYWGQGLTV TVSSGGGGSG GGGSGGGGSD IQMTQSPSSL 420 SASVGRDVTI TCRASQGISN YLNWYQQKPG KAPKPLIYTT SNLQSGVPSR FSGSGSGTDY 480 TLTISSLQPE DFATYYCMGQ TISSYTFGQG TKLEIKESKY GPPCPPCPMF WVLVVVGGVL 540 ACYSLLVTVA FIIFWKRGR KLLLYIFKQP FMRPVQTTQE EDGCSCRFPE EEEGGCELRV 600 KFSRSADAPA YQQGNQLYN ELNLGRREY DVLDKRRGRD PEMGGKPRK NPQEGLYNEL 660 QKDKMAEAYS EIGMKGERRR GKGDGLYQG LSTATKDTYD ALHMQLPPR 710 </pre>
3-85	<b>Sequences</b>	
3-85-1	Sequence Number [ID]	85
3-85-2	Molecule Type	DNA
3-85-3	Length	63
3-85-4	Features	<b>source 1..63</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-85-5	Residues	<pre> atggccttac cagtgaccgc ctgctcctg ccgctggcct tgctgctcca cgccgccagg 60 ccg 63 </pre>
3-86	<b>Sequences</b>	
3-86-1	Sequence Number [ID]	86
3-86-2	Molecule Type	DNA
3-86-3	Length	321
3-86-4	Features	<b>source 1..321</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-86-5	Residues	<pre> gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccagggga aagagccacc 60 ctctcctgca gggccagtc gagtgtagc agctacttag cctggtacca acagaacct 120 ggccaggctc ccaggctcct catctatgat gcaccaaca gggccactgg catcccagcc 180 aggttcagtg gcagtgggtc tgggacagac ttcactctca ccatacagcag cctagagcct 240 gaagatattg cagtttatta ctgtcagcag cgtagcaact ggccgatcac ctctggccaa 300 gggacacgac tggagattaa a 321 </pre>
3-87	<b>Sequences</b>	
3-87-1	Sequence Number [ID]	87
3-87-2	Molecule Type	DNA
3-87-3	Length	54
3-87-4	Features	<b>source 1..54</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-87-5	Residues	<pre> ggcagtacta gcggtggtgg ctccgggggc ggttccggtg ggggcggcag cagc 54 </pre>
3-88	<b>Sequences</b>	
3-88-1	Sequence Number [ID]	88

3-88-2	Molecule Type	DNA
3-88-3	Length	366
3-88-4	Features	<b>source 1..366</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
3-88-5	NonEnglishQualifier Value Residues	gaagtgcagc tggtaggagtc tgggggaggc ttggtacagc ctggcaggtc cctgagactc 60 tcctgtgcag cctctggatt cacctttaat gattatgcca tgcactgggt ccggcaagct 120 ccagggaaagg gcctggagtg ggtctcaact attagttgga atagtggttc cataggctat 180 gcgactctg tgaagggccg attcaccatc tccagagaca acgccaagaa gtcctctgtat 240 ctgcaaatga acagtctgag agctgaggac acggccttgt attactgtgc aaaagatata 300 cagtacggca actactacta cggtagggac gtctggggcc aagggaccac ggtcaccgctc 360 tcctca 366
<b>3-89</b>	<b>Sequences</b>	
3-89-1	Sequence Number [ID]	89
3-89-2	Molecule Type	DNA
3-89-3	Length	15
3-89-4	Features	<b>source 1..15</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
3-89-5	NonEnglishQualifier Value Residues	ggagggtggtg gatcc 15
<b>3-90</b>	<b>Sequences</b>	
3-90-1	Sequence Number [ID]	90
3-90-2	Molecule Type	DNA
3-90-3	Length	321
3-90-4	Features	<b>source 1..321</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
3-90-5	NonEnglishQualifier Value Residues	gacatccaga tgaccagtc ccctctctcc ctgtccgct ccgtgggcca ccgggtgacc 60 atcacctgcc gggcctccca gggcatctcc aactacctga actggtacca gcagaagccc 120 ggcaaggccc ccaagcccct gatctactac acctccaacc tgcagtcggt cgtgcctctc 180 cggttctccg gctccggctc cggcaccgac tacacctga ccatctctcc cctgcagccc 240 gaggacttcg ccacctacta ctgcatgggc cagaccatct cctcctacac cttcggccag 300 ggcaccaagc tggagatcaa g 321
<b>3-91</b>	<b>Sequences</b>	
3-91-1	Sequence Number [ID]	91
3-91-2	Molecule Type	DNA
3-91-3	Length	45
3-91-4	Features	<b>source 1..45</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
3-91-5	NonEnglishQualifier Value Residues	ggtggcggtg gctcgggagg tggtaggagtc ggtggcggcg gatct 45
<b>3-92</b>	<b>Sequences</b>	
3-92-1	Sequence Number [ID]	92
3-92-2	Molecule Type	DNA
3-92-3	Length	363
3-92-4	Features	<b>source 1..363</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
3-92-5	NonEnglishQualifier Value Residues	gaggtgcagc tggtaggagtc cggggcgggc ctggtgcagc ccggcgggtc cctgcggctg 60 tcctgcgccc cctcgggctt caccttctcc aacttcgaca tggcctgggt gcggcaggcc 120 cccggcaagg gcctgggtg ggtgtctctc atcaccaccg gcgcccacca cgccatctac 180 gccgactccg tgaagggccg gttcaccatc tcccgggaca acgccaagaa caccctgtac 240 ctgcagatga actcctcg gggcaggagc accgcccgtt actactgctg gcggcaggcc 300 tactacgacg gctaccact gttcagactac tggggccagg gcaccctggt gaccgtgtcc 360 tcc 363
<b>3-93</b>	<b>Sequences</b>	
3-93-1	Sequence Number [ID]	93
3-93-2	Molecule Type	DNA
3-93-3	Length	36
3-93-4	Features	<b>source 1..36</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
3-93-5	NonEnglishQualifier Value Residues	gagagcaagt acggaccgcc ctgccccct tgcctc 36
<b>3-94</b>	<b>Sequences</b>	

3-94-1	Sequence Number [ID]	94
3-94-2	Molecule Type	DNA
3-94-3	Length	84
3-94-4	Features	<b>source 1..84</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
3-94-5	NonEnglishQualifier Value	
	Residues	atgttctggg tgctggtggt ggtcggaggc gtgctggcct gctacagcct gctggtcacc 60 gtggccttca tcactctttg ggtg 84
<b>3-95</b>	<b>Sequences</b>	
3-95-1	Sequence Number [ID]	95
3-95-2	Molecule Type	DNA
3-95-3	Length	126
3-95-4	Features	<b>source 1..126</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
3-95-5	NonEnglishQualifier Value	
	Residues	aaacggggca gaaagaaact cctgtatata ttcaaacaac catttatgag accagtacaa 60 actactcaag aggaagatgg ctgtagctgc cgatttccag aagaagaaga aggaggatgt 120 gaactg 126
<b>3-96</b>	<b>Sequences</b>	
3-96-1	Sequence Number [ID]	96
3-96-2	Molecule Type	DNA
3-96-3	Length	336
3-96-4	Features	<b>source 1..336</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
3-96-5	NonEnglishQualifier Value	
	Residues	cgggtgaagt tcagcagaag cgccgacgcc cctgcctacc agcagggcca gaatcagctg 60 tacaacgagc tgaacctggg cagaagggaa gactacgacg tctctggataa gcggagagggc 120 cgggaccctg agatgggagg caagcctcgg cggaagaacc cccagggaagg cctgtataac 180 gaactgcaga aagacaagat ggccgagggc tacagcgaga tcggcatgaa gggcgagcgg 240 aggcggggca agggccacga cggcctgtat cagggcctgt ccaccgccac caaggatacc 300 tacgacgccc tgcacatgca ggcctgccc ccaagg 336
<b>3-97</b>	<b>Sequences</b>	
3-97-1	Sequence Number [ID]	97
3-97-2	Molecule Type	DNA
3-97-3	Length	2133
3-97-4	Features	<b>source 1..2133</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
3-97-5	NonEnglishQualifier Value	
	Residues	atggccttac cagtgaccgc cttgtctctg ccgctggcct tgctgtctcca cgccgccagg 60 cgggaaattg tgttgacaca gtctccagcc accctgtctt tgtctccagg ggaaagagcc 120 accctctcct gcagggccag tcagagtgtt agcagctact tagcctggta ccaacagaaa 180 cctggccagg ctcccaggct cctcatctat gatgcatcca acagggccac tggcatocca 240 gccagggtca gtggcagtggt gtctgggaca gacttcaactc tcaccatcag cagcctagag 300 cctgaagatt ttgcagttta ttactgtcag cagcgtagca actggccgat caccttcggc 360 caagggacac gactggagat taaaggcagt actagcggtg gtggctccgg gggcggttcc 420 ggtggggggcg gcagcagcga agtgacgctg gtggagtctg ggggagggctt ggtacagcct 480 ggcagggtccc tgagactctc ctgtgcagcc tctggattca cctttaatga ttatgccatg 540 cactgggtcc ggcaagctcc agggaagggc ctggagtggg tctcaactat tagttggaat 600 agtggttcca taggctatgc ggactctgtg aagggccgat tcaccatctc cagagacaac 660 gccaagaagt ccctgtatct gcaaatgaac agtctgagag ctgaggacac ggccttgtat 720 tactgtgcaa aagatataca gtacggcaac tactactacg gtatggacgt ctggggccaa 780 gggaccacgg tcaccgtctc ctcaggaggt ggtggatccg acatccagat gaccagctcc 840 ccctcctccc tgtccgctc cgtgggcgac cgggtgacca tcaccctgccc ggcctcccag 900 ggcatctcca actacctgaa ctgggtaccag cagaagcccc gcaaggcccc caagcccctg 960 atctactaca cctccaact gcagtcggc gtgccctccc ggttctccgg ctccggctcc 1020 ggcaccgact acaccctgac catctcctcc ctgcagccc aggactctgc cacctactac 1080 tgcatggggc agaccatctc ctccatcacc ttccggccagg gcaccaagct ggagatcaag 1140 ggtggcggtg gctcggggcg tgggtgggtg ggtggcggcg gatctgaggt gcagctgggt 1200 gagtccggcg gcggcctggt gcagcccgcc ggtccctgc ggtctcctg ccgcccctcc 1260 ggcttcacct tctccaactt cgacatggcc tgggtgcgcc agggcccccg caagggctctg 1320 gtgtgggtgt cctccatcac caccggcgcc gaccacgcca tctacgcca ctccgtgaag 1380 ggccgggtca ccatctccc ggacaacgcc aagaacaacc tgtacctgca gatgaactcc 1440 ctgcggggcg aggacaccgc cgtgtactac tgcgtgccc acggctacta cgacggctac 1500 cacctgttcg actactgggg ccagggcacc ctggtgaccg tgtcctccga gagcaagtac 1560 ggaccgccct gcccccctg ccctatgttc tgggtgctg tggtgtctg aggcgtgctg 1620 gcctgctaca gcctgctggt caccgtggcc ttoatcatct tttgggtgaa acggggcaga 1680 aagaaactcc tgtatataatt caaacaacca tttatgagac cagtacaaac tactcaagag 1740 gaagatggct gtagctgccc atttccagaa gaagaagaag gaggatgtga actgcgggtg 1800

		<p>aagttcagca gaagcgcgca cgccccctgcc taccagcagg gccagaatca gctgtacaac 1860  gagctgaacc tgggcagaag ggaagagtac gacgtcctgg ataagcggag aggccgggac 1920  cctgagatgg gcggcaagcc tcggcggaag aacccccagg aaggcctgta taacgaactg 1980  cagaaagaca agatggccga gccctacagc gagatcggca tgaagggcga gcggagggcg 2040  ggcaagggcc acgacggcct gtatcagggc ctgtccaccg ccaccaagga tacctacgac 2100  gcctgcaca tgcaggcct gcccccagg taa 2133</p>
<b>3-98</b>	<b>Sequences</b>	
3-98-1	Sequence Number [ID]	98
3-98-2	Molecule Type	AA
3-98-3	Length	710
3-98-4	Features	<b>source 1..710</b>
	Location/Qualifiers	mol_type=protein organism=synthetic construct
	NonEnglishQualifier Value	
3-98-5	Residues	<p>MALPVTALLL PLALLLHAAR PEIVLTQSPA TSLSPGERA TLSCRASQSV SSYLAWYQQK 60  PGQAPRLLIY DASNRATGIP ARFSGSGSGT DFTLTISLE PEDFAVYCYQ QRSNWPITFG 120  QGTRELEIKGS TSGGSGGGS GGGGSSEVQL VESGGGLVQP GRSLRLSCAA SGFTFNDYAM 180  HWRQAPGKG LEWVSTISWN SGSIGYADSV KGRFTISRDN AKKSLYLQMN SLRAEDTALY 240  YCAKDIQYGN YYGMDVWQO GTTVTVSSGG GSDIQMTQS PSSLSASVGD RVTITCRASQ 300  GISNYLNWYQ QKPGKAPKPL IYYSNLQSG VPSRFSGSGS GTDYTLTISS LQPEDFATYY 360  CMGQTISSYT FGQGTKLEIK GGGSGGGGS GGGGSEVQLV ESGGGLVQPG GSLRLSCAAS 420  GFTFSNFDMA WVRQAPGKGL VWVSSITGA DHAIYADSVK GRFTISRDNA KNTLYLQMNS 480  LRAEDTAVYY CVRHGYDGY HLFDYWQGT LVTVSSESKY GPCCPPCPMF WVLVVGGVL 540  ACYSLLVTVF FIFWVKRGR KLLLYIFKQP FMRPVQTQE EDGCSCRFPE EEEGGCELRV 600  KFSRSADAPA YQQGQNQLYN ELNLGRREY DVLDKRRGRD PEMGGKPRK NPQEGLYNEL 660  QDKMAEAYS EIGMKGERR GKGDGLYQG LSTATKDTYD ALHMQUALPPR 710</p>
<b>3-99</b>	<b>Sequences</b>	
3-99-1	Sequence Number [ID]	99
3-99-2	Molecule Type	DNA
3-99-3	Length	63
3-99-4	Features	<b>source 1..63</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-99-5	Residues	<p>atggccttac cagtgaccgc ctgctcctg ccgctggcct tgctgctcca cgccgccagg 60  ccg 63</p>
<b>3-100</b>	<b>Sequences</b>	
3-100-1	Sequence Number [ID]	100
3-100-2	Molecule Type	DNA
3-100-3	Length	366
3-100-4	Features	<b>source 1..366</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-100-5	Residues	<p>gaagtgcagc tgggtggagtc tgggggaggc ttggtacagc ctggcaggtc cctgagactc 60  tcctgtgcag cctctggatt cacctttaat gattatgccca tgcactgggt ccggcaagct 120  ccaggaaggg gcctggagtg ggtctcaact attagttgga atagtggttc cataggtat 180  gcgactctg tgaagggccg atccaccatc tccagagaca acgccaagaa gtccctgtat 240  ctgcaaatga acagtctgag agctgaggac acggcctgt attactgtgc aaaagatata 300  cagtacggca actactacta cggtatggac gtctggggcc aagggaccac ggtcaccgtc 360  tcctca 366</p>
<b>3-101</b>	<b>Sequences</b>	
3-101-1	Sequence Number [ID]	101
3-101-2	Molecule Type	DNA
3-101-3	Length	54
3-101-4	Features	<b>source 1..54</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-101-5	Residues	<p>ggcagtacta gcggtggtgg ctccgggggc ggttccggtg gggggcgcag cagc 54</p>
<b>3-102</b>	<b>Sequences</b>	
3-102-1	Sequence Number [ID]	102
3-102-2	Molecule Type	DNA
3-102-3	Length	321
3-102-4	Features	<b>source 1..321</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-102-5	Residues	<p>gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccagggga aagagccacc 60  ctctcctgca gggccagtc gagtggtagc agctacttag cctggtacca acagaaacct 120  ggccaggctc ccaggctcct catctatgat gcatccaaca gggccactgg catccagcc 180</p>

		aggttcagtg gcagtggtg tgggacagac ttcactctca ccatcagcag cctagagcct 240 gaagattttg cagtttatta ctgtcagcag cgtagcaact ggccgatcac cttcggccaa 300 gggacacgac tggagattaa a 321
<b>3-103</b>	<b>Sequences</b>	
3-103-1	Sequence Number [ID]	103
3-103-2	Molecule Type	DNA
3-103-3	Length	15
3-103-4	Features	<b>source 1..15</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-103-5	Residues	ggaggtggtg gatcc 15
<b>3-104</b>	<b>Sequences</b>	
3-104-1	Sequence Number [ID]	104
3-104-2	Molecule Type	DNA
3-104-3	Length	321
3-104-4	Features	<b>source 1..321</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-104-5	Residues	gacatccaga tgaccagtc cccctcctcc ctgtccgct ccgtgggcga ccgggtgacc 60 atcaoctgcc gggcctcca gggcatctcc aactacctga actggtacca gcagaagccc 120 ggcaaggccc ccaagccct gatctactac acctccaacc tgcagtcagg cgtgcctcc 180 cgttctccg gctccggctc cggcaccgac tacacctga ccatctctc cctgcagccc 240 gaggacttcg ccacctacta ctgcatgggc cagaccatct cctcctacac cttcggccag 300 ggcaccaagc tggagatcaa g 321
<b>3-105</b>	<b>Sequences</b>	
3-105-1	Sequence Number [ID]	105
3-105-2	Molecule Type	DNA
3-105-3	Length	45
3-105-4	Features	<b>source 1..45</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-105-5	Residues	ggtggcggtg gctcgggcgg tgggtgggtcg ggtggcgcg gatct 45
<b>3-106</b>	<b>Sequences</b>	
3-106-1	Sequence Number [ID]	106
3-106-2	Molecule Type	DNA
3-106-3	Length	363
3-106-4	Features	<b>source 1..363</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-106-5	Residues	gaggtgcagc tgggtggagtc cggcggcggc ctggtgcagc ccggcggtc cctgcggctg 60 tcctgcgccc cctccggctt caccttctcc aacttcgaca tggcctgggt gcggcaggcc 120 cccggcaagg gcctggtgtg ggtgtctcc atcaccaccg gcgcccacca cgccatctac 180 gccgactccg tgaagggccg gttcaccatc tccgggaca acgccaagaa caccctgtac 240 ctgcagatga actccctcgg gcccgaggac accgcccgtg actactcgt gcggcacggc 300 tactacgagc gtaccacct gttcgactac tggggccagg gcacctgggt gaccgtgtcc 360 tcc 363
<b>3-107</b>	<b>Sequences</b>	
3-107-1	Sequence Number [ID]	107
3-107-2	Molecule Type	DNA
3-107-3	Length	36
3-107-4	Features	<b>source 1..36</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-107-5	Residues	gagagcaagt acggaccgcc ctgccccct tgcct 36
<b>3-108</b>	<b>Sequences</b>	
3-108-1	Sequence Number [ID]	108
3-108-2	Molecule Type	DNA
3-108-3	Length	84
3-108-4	Features	<b>source 1..84</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-108-5	Residues	atgttctggg tgcgtggtg gtcggaggc gtgctggcct gctacagcct gctggtcacc 60 gtggccttca tcatctttg ggtg 84
<b>3-109</b>	<b>Sequences</b>	

3-109-1	Sequence Number [ID]	109
3-109-2	Molecule Type	DNA
3-109-3	Length	126
3-109-4	Features	<b>source 1..126</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
3-109-5	NonEnglishQualifier Value Residues	aaacggggca gaagaaact cctgtatata ttcaaacaac catttatgag accagtataa 60 actactcaag aggaagatgg ctgtagctgc cgatttccag aagaagaaga aggaggatgt 120 gaactg 126
<b>3-110</b>	<b>Sequences</b>	
3-110-1	Sequence Number [ID]	110
3-110-2	Molecule Type	DNA
3-110-3	Length	336
3-110-4	Features	<b>source 1..336</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
3-110-5	NonEnglishQualifier Value Residues	cgggtgaagt tcagcagaag cgcgcagccc cctgcctacc agcaggggcca gaatcagctg 60 tacaacgagc tgaacctggg cagaagggaa gagtacgacg tccctggataa gcggagagggc 120 cgggaccctg agatgggcgg caagcctcgg cggagaagaacc cccaggaagg cctgtataac 180 gaactgcaga aagacaagat ggccgagggc tacagcgaga tcggcatgaa gggcgagcgg 240 aggcggggca agggccacga cggcctgtat cagggcctgt ccaccgccac caaggatacc 300 tacgacgccc tgcacatgca ggcctgccc ccaagg 336
<b>3-111</b>	<b>Sequences</b>	
3-111-1	Sequence Number [ID]	111
3-111-2	Molecule Type	DNA
3-111-3	Length	2133
3-111-4	Features	<b>source 1..2133</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
3-111-5	NonEnglishQualifier Value Residues	atggccttac cagtgaccgc cttgctcctg ccgctggcct tgcctgctcca cgcccagcag 60 ccggaagtgc agctgggtgga gtctggggga ggcttggtac agcctggcag gtcccctgaga 120 ctctcctgtg cagcctctgg attcacctt aatgattatg ccatgcactg ggtccggcaa 180 gctccaggga agggcctgga gtgggtctca actattagtt ggaatagtggt ttccatagggc 240 tatgoggact ctgtgaaggg ccgattcacc atctccagag acaaccgcaa gaagtcctcg 300 tatctgcaaa tgaacagtct gagagctgag gacacggcct tgtattactg tgcaaaagat 360 atacagtagc gcaactacta ctacggtagt gacgtctggg gccaaaggac cacggtcacc 420 gtctcctcag gcagtagtag cggtggtggc tccggggggc gttccggctg gggcggcagc 480 agcgaatg tgttgacaca gtctccagcc accctgtcct tgcctccagg ggaaagagcc 540 accctctcct gcagggccag tcagagtgtt agcagctact tagcctggta ccaacagaaa 600 cctggccagg ctcccaggct cctcatctat gatgcacca acagggcccac tggcatocca 660 gccaggttca gtggcagtgg gtctgggaca gacttcaact tcaccatcag cagcctagag 720 cctgaagatt ttgcagttta ttactgtcag cagcgtagca actggccgat cacctcggc 780 caagggacac gactggagat taaaggaggt ggtggatccg acatccagat gaccagctcc 840 ccctcctccc tgtccgctc cgtggggcag cgggtgacca tcacctgccg ggcctcccag 900 ggcatctcca actacctgaa ctggtagcag cagaagcccg gcaaggcccc caagcccctg 960 atctactaca cctccaacct gcagtcgggc gtgccctccc ggttctccgg ctccggctcc 1020 ggcaaccgact aaccctgac catctcctcc ctgcagcccg aggacttcgc cacctactac 1080 tgcattggcc agaccatctc ctctacacc ttcggccagg gcaccaagct ggagatcaag 1140 ggtggcggtg gctcggggcg tggtggtcg ggtggcggcg gatctgaggt gcagctgggtg 1200 gagtccggcg gcggcctggt gcagcccggc ggctccctgc ggctgtcctg cgcccctcc 1260 ggcttcacct tctccaactt cgacatggcc tgggtgcccg agggcccccg caaggcctg 1320 gtgtgggtgt cctccatcac caccggcgcg gaccacgcca tctacgccga ctccgtgaag 1380 ggccgggttca ccatctcccg ggacaacgcc aagaacacc tgtacctgca gatgaactcc 1440 ctgcggggcg aggacaccgc cgtgtactac tgcgtgcggc acggctacta cgacggctac 1500 cacctgttcg actactgggg ccagggcacc ctggtagacc tgcctccga gagcaagtac 1560 ggaccgcctt gcccccttg ccctatgttc tgggtgctgg tgggtgctcg aggcgtgctg 1620 gcctgctaca gcctgctggt caccgtggcc ttcattcatct tttgggtgaa acggggcaga 1680 aagaaactcc tgtatatatt caaacaacca tttatgagac cagtacaaac tactcaagag 1740 gaagatggct gtactgcccg atttccagaa gaagaagaag gaggatgtga actgcccgggtg 1800 aagttcagca gaagcggcga cgcctcctgc taccagcagg gccagaatca gctgtacaac 1860 gagctgaacc tgggcagaag ggaagagtag gacgtcctgg ataaggcggag aggcggggag 1920 cctgagatgg gcggcaagcc tcggcgggag aacccccagg aaggcctgta taacgaactg 1980 cagaaagaca agatggccga ggccacagc gagatcggca tgaaggggcga gcggagggcg 2040 ggcaagggcc acgacggcct gtatcagggc ctgtccaccg ccaccaagga tacctacgac 2100 gcctgcaca tgcaggccct gcccccaagg taa 2133
<b>3-112</b>	<b>Sequences</b>	
3-112-1	Sequence Number [ID]	112
3-112-2	Molecule Type	AA
3-112-3	Length	710
3-112-4	Features	<b>source 1..710</b>

	Location/Qualifiers	mol_type=protein organism=synthetic construct	
3-112-5	NonEnglishQualifier Value Residues	MALPVTALLL PLALLLHAAR PEVQLVESGG GLVQPGRSLR LSCAASGFTF NDYAMHWVRQ 60 APGKGLEWVS TISWNSGSIG YADSVKGRFT ISRDNAKKS LYLQMNLSRAE DTALYYCAKD 120 IQYGNYYGM DVWGQGTTVT VSSGSTSGGG SGGSGGGGS SEIVLTQSPA TLSLSPGERA 180 TLSCRASQSV SSYLAWYQK PQQAPRLLIY DASNRATGIP ARFSGSGSGT DFTLTISSE 240 PEDFAVYYCQ QRSNWPITFG QGTRLEIKGG GGSDIQMTQS PSSLSASVGD RVTITCRASQ 300 GISNYLNWYQ QKPGKAPKPL IYYTSNLQSG VPSRFSGSGS GTDYTLTISS LQPEDFATYY 360 CMGQTISSYT FGQGTKLEIK GGGSGGGGS GGGGSEVQLV ESGGGLVQPG GSLRLSCAAS 420 GFTFSNFDMA WVRQAPGKGL VWVSSITGA DHAIYADSVK GRFTISRDNA KNTLYLQMNS 480 LRAEDTAVYY CVRHGYDGY HLFDYWGQGT LVTVSSESKY GPCCPPCPMF WVLVVVGGVL 540 ACYSLLVTV FIFWVKRGR KLLLYIFKQP FMRPVQTQE EDGCSCRFPE EEEGGCELRV 600 KFSRSADAPA YQQGQNQLYN ELNLGRREEY DVLDKRRGRD PEMGGKPRK NPQEGLYNEL 660 QKDKMAEAYS EIGMKGERRR GKGHDGLYQG LSTATKDTYD ALHMQUALPPR 710	
<b>3-113</b>	<b>Sequences</b>		
3-113-1	Sequence Number [ID]	113	
3-113-2	Molecule Type	DNA	
3-113-3	Length	63	
3-113-4	Features	<b>source 1..63</b>	
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct	
	NonEnglishQualifier Value		
3-113-5	Residues	atggccttac cagtgaccgc ctgctctctg ccgctggcct tgctgctcca cgccgccagg 60 ccg 63	
<b>3-114</b>	<b>Sequences</b>		
3-114-1	Sequence Number [ID]	114	
3-114-2	Molecule Type	DNA	
3-114-3	Length	366	
3-114-4	Features	<b>source 1..366</b>	
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct	
	NonEnglishQualifier Value		
3-114-5	Residues	gaagtgcagc tgggtggagtc tgggggaggc ttggtacagc ctggcaggtc cctgagactc 60 tcctgtgcag cctctggatt cacctttaat gattatgcc a tgcactgggt ccggcaagct 120 ccagggaagg gcctggagtg ggtctcaact attagttgga atagtggttc cataggtcat 180 gcgactctg tgaagggccg attcaccatc tccagagaca acgccaagaa gtcctctgat 240 ctgcaaatga acagtctgag agctgaggac acggccttgt attactgtgc aaaagatata 300 cagtacggca actactacta cggtatggac gtctggggcc aagggaccac ggtcaccgtc 360 tcctca 366	
<b>3-115</b>	<b>Sequences</b>		
3-115-1	Sequence Number [ID]	115	
3-115-2	Molecule Type	DNA	
3-115-3	Length	54	
3-115-4	Features	<b>source 1..54</b>	
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct	
	NonEnglishQualifier Value		
3-115-5	Residues	ggcagtaacta gcggtgggtg ctccgggggc ggttccggtg ggggcccag cagc 54	
<b>3-116</b>	<b>Sequences</b>		
3-116-1	Sequence Number [ID]	116	
3-116-2	Molecule Type	DNA	
3-116-3	Length	321	
3-116-4	Features	<b>source 1..321</b>	
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct	
	NonEnglishQualifier Value		
3-116-5	Residues	gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccagggga aagagccacc 60 ctctctgca gggccagtc gagtgtagc agtacttag cctggtagca acagaaacct 120 ggccaggctc ccaggctcct catctatgat gcatccaaca gggccactgg catcccagcc 180 aggttcagtg gcagtgggtc tgggacagac ttcaactctca ccatcagcag cctagagcct 240 gaagattttg cagtttatta ctgtcagcag cgtagcaact ggccgatcac cttcggccaa 300 gggacacgac tggagattaa a 321	
<b>3-117</b>	<b>Sequences</b>		
3-117-1	Sequence Number [ID]	117	
3-117-2	Molecule Type	DNA	
3-117-3	Length	15	
3-117-4	Features	<b>source 1..15</b>	
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct	
	NonEnglishQualifier Value		

3-117-5	Residues	ggaggtggtg gatcc	15
<b>3-118</b>	<b>Sequences</b>		
3-118-1	Sequence Number [ID]	118	
3-118-2	Molecule Type	DNA	
3-118-3	Length	363	
3-118-4	Features	<b>source 1..363</b>	
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct	
	NonEnglishQualifier Value		
3-118-5	Residues	gaggtgcagc tggtaggtc cggcggcggc ctggtgcagc ccggcggctc cctgcggctg 60 tcctgcgcgc cctccggctt caccttctcc aacttcgaca tggcctgggt gcggcaggcc 120 cccggcaagg gcctggtgtg ggtgtcctcc atcaccaccg gcgcccacca cgccatctac 180 gccgactccg tgaagggccg gttcaccatc tcccgggaca acgccaagaa caccctgtac 240 ctgcagatga actccctgcg ggccgaggac accgcccgtg actactgcgt gcggcacggc 300 tactacgacg gctaccacct gttcgactac tggggccagg gcaccctggt gaccgtgtcc 360 tcc 363	
<b>3-119</b>	<b>Sequences</b>		
3-119-1	Sequence Number [ID]	119	
3-119-2	Molecule Type	DNA	
3-119-3	Length	45	
3-119-4	Features	<b>source 1..45</b>	
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct	
	NonEnglishQualifier Value		
3-119-5	Residues	ggtggcgggtg gctcgggcgg tggtaggtcg ggtggcggcg gatct	45
<b>3-120</b>	<b>Sequences</b>		
3-120-1	Sequence Number [ID]	120	
3-120-2	Molecule Type	DNA	
3-120-3	Length	321	
3-120-4	Features	<b>source 1..321</b>	
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct	
	NonEnglishQualifier Value		
3-120-5	Residues	gacatccaga tgaccagtc cccctcctcc ctgtccgct ccgtgggcga ccgggtgacc 60 atcaoctgcc gggcctcca gggcatctcc aactacctga actggtacca gcagaagccc 120 ggcaaggccc ccaagcccct gatctactac acctccaacc tgcagtccgg cgtgcctcc 180 cgttctccg gctccggctc cggcaccgac tacacctga ccatctctc cctgcagccc 240 gaggacttcg ccacctacta ctgcatgggc cagaccatct cctcctacac cttcggccag 300 ggcacciaagc tggagatcaa g 321	
<b>3-121</b>	<b>Sequences</b>		
3-121-1	Sequence Number [ID]	121	
3-121-2	Molecule Type	DNA	
3-121-3	Length	36	
3-121-4	Features	<b>source 1..36</b>	
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct	
	NonEnglishQualifier Value		
3-121-5	Residues	gagagcaagt acggaccgcc ctgccccct tgcct	36
<b>3-122</b>	<b>Sequences</b>		
3-122-1	Sequence Number [ID]	122	
3-122-2	Molecule Type	DNA	
3-122-3	Length	84	
3-122-4	Features	<b>source 1..84</b>	
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct	
	NonEnglishQualifier Value		
3-122-5	Residues	atgttctggg tgctggtggt ggtcggaggc gtgctggct gctacagcct gctggtcacc 60 gtggccttca tcatctttg ggtg	84
<b>3-123</b>	<b>Sequences</b>		
3-123-1	Sequence Number [ID]	123	
3-123-2	Molecule Type	DNA	
3-123-3	Length	126	
3-123-4	Features	<b>source 1..126</b>	
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct	
	NonEnglishQualifier Value		
3-123-5	Residues	aaacggggca gaaagaaact cctgtatata ttcaaacaac catttatgag accagtacaa 60 actactcaag aggaagatgg ctgtagctgc cgatttccag aagaagaaga aggaggatgt 120 gaactg 126	
<b>3-124</b>	<b>Sequences</b>		

3-124-1	Sequence Number [ID]	124
3-124-2	Molecule Type	DNA
3-124-3	Length	336
3-124-4	Features	<b>source 1..336</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-124-5	Residues	cgggtgaagt tcagcagaag cgccgacgcc cctgcctacc agcaggggcca gaatcagctg 60 tacaacgagc tgaacctggg cagaagggaa gagtacgacg tccctggataa gcgagagaggc 120 cgggaccctg agatggggcg caagcctcgg cggaagaacc cccaggaagg cctgtataac 180 gaactgcaga aagacaagat ggccgagggc tacagcgaga tcggcatgaa gggcgagcgg 240 aggcggggca agggccacga cggcctgtat cagggctgt ccaccgccac caaggatacc 300 tacgacgccc tgcacatgca ggccctgccc ccaagg 336
<b>3-125</b>	<b>Sequences</b>	
3-125-1	Sequence Number [ID]	125
3-125-2	Molecule Type	DNA
3-125-3	Length	2133
3-125-4	Features	<b>source 1..2133</b>
	Location/Qualifiers	mol_type=other DNA organism=synthetic construct
	NonEnglishQualifier Value	
3-125-5	Residues	atggccttac cagtgaccgc cttgctcctg ccgctggcct tgcctgctcca cgccgccagg 60 ccggaagtgc agctgggtga gtctggggga ggcttggtac agcctggcag gtccctgaga 120 ctctcctgtg cagcctctgg atccaccttt aatgattatg ccatgacctg ggtccggcaa 180 gctccaggga agggcctgga gtgggtctca actattagtt ggaatagttg ttccatagggc 240 tatgctggact ctgtgaaggg ccgattcacc atctccagag acaacgcca gaagtccctg 300 tatctgcaaa tgaacagtct gagagctgag gacacggcct tgtattactg tgcaaaagat 360 atacagtagc gcaactacta ctacggtagt gacgtctggg gccaaaggac cacggtcacc 420 gtctcctcag gcagtagtag cggtaggtggc tccggggggcg gttccgggtgg gggcggcagc 480 agcgaagtgc tggtagacac gtctccagcc accctgtctt tgcctccagg ggaagagaggc 540 accctctcct gcagggccag tcagagtgtt agcagctact tagcctggta ccaacagaaa 600 cctggccagg ctcccaggct cctcatctat gatgcatcca acagggccac tggcatocca 660 gccaggttca gtggcagtggt gtctgggaca gacttcaact tcaccatcag cagcctagag 720 cctgaagatt ttgcagttta ttactgtcag cagcgtagca actggccgat caccttcggc 780 caagggacac gactggagat taaaggaggt ggtggatccg aggtgcagct ggtggagtcc 840 ggcggcggcc tggtagacgc cggcggctcc ctgctggctgt cctgcgccgc ctccggcttc 900 accttctcca acctgcacat ggctgggtgg cggcaggccc ccggcaaggg cctgggtgtg 960 gtgtcctcca tcaccaccgg cgccgaccac gccatctact ccagctccgt gaaggcccg 1020 ttcaccatct cccgggacaa cgccaagaac accctgtacc tgcagatgaa ctccctgcgg 1080 gccgaggaca ccgctgtgta ctactgcgtg cggcacggct actacgacgg ctaccacctg 1140 ttcgactact ggggccaggg cacctcgttg acogtctcct ccgggtggcg tggctcgggc 1200 ggtggtgggt cgggtggcgg cggatctgac atccagatga cccagtcacc ctccctccctg 1260 tccgctcctg tggcgacccg ggtgacctc acctgccggg cctcccaggg catctccaac 1320 tacctgaact ggtaccagca gaagcccggc aaggccccc agccctctat ctactacacc 1380 tccaacctgc agtccggcgt gccctcccgg ttctccggct ccggctccgg caccgactac 1440 accctgacca tctcctcctt gcagcccag gacttcgcca cctactactg catgggcccag 1500 accatctcct cctacacctt cggccagggc accaagctgg agatcaagga gagcaagtag 1560 ggacogccct gccccccttg ccctatgttc tgggtgctgg tgggtgctcg aggcgtgctg 1620 gcctgctaca gcctgctggt caccgtggcc ttcacatctt tttgggtgaa acggggcaga 1680 aagaaactcc tgtatatatt caaacaacca tttatgagac cagtacaaac tactcaagag 1740 gaagatggct gtagctgccc atttccagaa gaagaagaag gaggatgtga actgcgggtg 1800 aagttcagca gaagcgcgca cgcccctgcc tacagcagg gccagaatca gctgtacaac 1860 gagctgaacc tgggcagaag ggaagagtac gacgtcctgg ataagcggag aggcggggac 1920 cctgagatgg gcggcaagcc tcggcggaag aacccccagg aaggcctgta taacgaactg 1980 cagaaagaca agatggccga ggctacagc gagatcgcca tgaagggcga gcggagggcg 2040 ggcaagggcc acgacggcct gtatcagggc ctgtccaccg ccaccaagga tacctacgac 2100 gcctgcaca tgcaggcctt gcccccagg taa 2133
<b>3-126</b>	<b>Sequences</b>	
3-126-1	Sequence Number [ID]	126
3-126-2	Molecule Type	AA
3-126-3	Length	710
3-126-4	Features	<b>source 1..710</b>
	Location/Qualifiers	mol_type=protein organism=synthetic construct
	NonEnglishQualifier Value	
3-126-5	Residues	MALPVTALLL PLALLLHAAR PEVQLVESGG GLVQPGRSLR LSCAASGFTF NDYAMHWVRQ 60 APGKGLEWVS TISWNSGSIG YADSVKGRFT ISRDNAAKSL YLQMNLSRAE DTALYYCAKD 120 IQYGNYYYGM DVWGQGTIVT VSSGSTSGGG SGGGSGGGGS SEIVLTQSPA TLSLSPGERA 180 TLSCRASQSV SSYLAWYQQK PQQAPRLLIY DASNRATGIP ARFSGSGSGT DFTLTISSLE 240 PEDFAVYYCQ QRSNWPITFG QGTRLEIKGG GGSEVQLVES GGGLVQPGGS LRLSCAASGF 300 TFSNFDMAWV RQAPGKGLVW VSSITGADH AIYADSVKGR FTISRDNAAK TLYLQMNLSR 360 AEDTAVYYCV RHGYDDGYHL FDYWGQTLV TVSSGGGGSG GGSGGGGSD IQMTQSPSSL 420 SASVGDRTVI TCRASQGISN YLNWYQQKPG KAPKPLIYYT SNLQSGVPSR FSGSGSGTDY 480

		TLTISSLQPE DFATYYCMGQ TISSYTFGQG TKLEIKESKY GPPCPCPMF WVLVVGGVL 540 ACYSLLVTVVA FIIFWVKRGR KLLYIFKQP FMRPVQTTQE EDGCSCRFPE EEEGGCELRV 600 KFSRSADAPA YQQGQNQLYN ELNLGRREY DVLDKRRGRD PEMGGKPRK NPQEGLYNEL 660 QKDKMAEAYS EIGMKGERRR GKGDGLYQG LSTATKDTYD ALHMQUALPPR 710
<b>3-127</b>	<b>Sequences</b>	
3-127-1	Sequence Number [ID]	127
3-127-2	Molecule Type	AA
3-127-3	Length	6
3-127-4	Features	<b>source 1..6</b>
	Location/Qualifiers	mol_type=protein organism=synthetic construct
	NonEnglishQualifier Value	
3-127-5	Residues	NDYAMH 6
<b>3-128</b>	<b>Sequences</b>	
3-128-1	Sequence Number [ID]	128
3-128-2	Molecule Type	AA
3-128-3	Length	17
3-128-4	Features	<b>source 1..17</b>
	Location/Qualifiers	mol_type=protein organism=synthetic construct
	NonEnglishQualifier Value	
3-128-5	Residues	TISWNSGSIG YADSVKG 17
<b>3-129</b>	<b>Sequences</b>	
3-129-1	Sequence Number [ID]	129
3-129-2	Molecule Type	AA
3-129-3	Length	13
3-129-4	Features	<b>source 1..13</b>
	Location/Qualifiers	mol_type=protein organism=synthetic construct
	NonEnglishQualifier Value	
3-129-5	Residues	DIQYGNYYYG MDV 13
<b>3-130</b>	<b>Sequences</b>	
3-130-1	Sequence Number [ID]	130
3-130-2	Molecule Type	AA
3-130-3	Length	11
3-130-4	Features	<b>source 1..11</b>
	Location/Qualifiers	mol_type=protein organism=synthetic construct
	NonEnglishQualifier Value	
3-130-5	Residues	RASQSVSSYL A 11
<b>3-131</b>	<b>Sequences</b>	
3-131-1	Sequence Number [ID]	131
3-131-2	Molecule Type	AA
3-131-3	Length	7
3-131-4	Features	<b>source 1..7</b>
	Location/Qualifiers	mol_type=protein organism=synthetic construct
	NonEnglishQualifier Value	
3-131-5	Residues	DASNRAT 7
<b>3-132</b>	<b>Sequences</b>	
3-132-1	Sequence Number [ID]	132
3-132-2	Molecule Type	AA
3-132-3	Length	9
3-132-4	Features	<b>source 1..9</b>
	Location/Qualifiers	mol_type=protein organism=synthetic construct
	NonEnglishQualifier Value	
3-132-5	Residues	QQR.SNWPI.T 9
<b>3-133</b>	<b>Sequences</b>	
3-133-1	Sequence Number [ID]	133
3-133-2	Molecule Type	AA
3-133-3	Length	23
3-133-4	Features	<b>source 1..23</b>
	Location/Qualifiers	mol_type=protein organism=synthetic construct
	NonEnglishQualifier Value	
3-133-5	Residues	DIQMTQSPSS LSASVGRVT ITC 23
<b>3-134</b>	<b>Sequences</b>	

3-134-1	Sequence Number [ID]	134	
3-134-2	Molecule Type	AA	
3-134-3	Length	11	
3-134-4	Features	<b>source 1..11</b>	
	Location/Qualifiers	mol_type=protein organism=synthetic construct	
	NonEnglishQualifier Value		
3-134-5	Residues	RASQGISNYL N	11
<b>3-135</b>	<b>Sequences</b>		
3-135-1	Sequence Number [ID]	135	
3-135-2	Molecule Type	AA	
3-135-3	Length	15	
3-135-4	Features	<b>source 1..15</b>	
	Location/Qualifiers	mol_type=protein organism=synthetic construct	
	NonEnglishQualifier Value		
3-135-5	Residues	WYQQKPGKAP KPLIY	15
<b>3-136</b>	<b>Sequences</b>		
3-136-1	Sequence Number [ID]	136	
3-136-2	Molecule Type	AA	
3-136-3	Length	7	
3-136-4	Features	<b>source 1..7</b>	
	Location/Qualifiers	mol_type=protein organism=synthetic construct	
	NonEnglishQualifier Value		
3-136-5	Residues	YTSNLQS	7
<b>3-137</b>	<b>Sequences</b>		
3-137-1	Sequence Number [ID]	137	
3-137-2	Molecule Type	AA	
3-137-3	Length	32	
3-137-4	Features	<b>source 1..32</b>	
	Location/Qualifiers	mol_type=protein organism=synthetic construct	
	NonEnglishQualifier Value		
3-137-5	Residues	GVPSRFSGSG SGTDYTLTIS SLQPEDFATY YC	32
<b>3-138</b>	<b>Sequences</b>		
3-138-1	Sequence Number [ID]	138	
3-138-2	Molecule Type	AA	
3-138-3	Length	9	
3-138-4	Features	<b>source 1..9</b>	
	Location/Qualifiers	mol_type=protein organism=synthetic construct	
	NonEnglishQualifier Value		
3-138-5	Residues	MGQTISSYT	9
<b>3-139</b>	<b>Sequences</b>		
3-139-1	Sequence Number [ID]	139	
3-139-2	Molecule Type	AA	
3-139-3	Length	10	
3-139-4	Features	<b>source 1..10</b>	
	Location/Qualifiers	mol_type=protein organism=synthetic construct	
	NonEnglishQualifier Value		
3-139-5	Residues	FGQGTKLEIK	10
<b>3-140</b>	<b>Sequences</b>		
3-140-1	Sequence Number [ID]	140	
3-140-2	Molecule Type	AA	
3-140-3	Length	30	
3-140-4	Features	<b>source 1..30</b>	
	Location/Qualifiers	mol_type=protein organism=synthetic construct	
	NonEnglishQualifier Value		
3-140-5	Residues	EVQLVESGGG LVQPGGSLRL SCAASGFTFS	30
<b>3-141</b>	<b>Sequences</b>		
3-141-1	Sequence Number [ID]	141	
3-141-2	Molecule Type	AA	
3-141-3	Length	5	
3-141-4	Features	<b>source 1..5</b>	
	Location/Qualifiers	mol_type=protein	

3-141-5	NonEnglishQualifier Value Residues	organism=synthetic construct NFDMA	5
<b>3-142</b>	<b>Sequences</b>		
3-142-1	Sequence Number [ID]	142	
3-142-2	Molecule Type	AA	
3-142-3	Length	14	
3-142-4	Features Location/Qualifiers	<b>source 1..14</b> mol_type=protein organism=synthetic construct	
3-142-5	NonEnglishQualifier Value Residues	WVRQAPGKGL VWVS	14
<b>3-143</b>	<b>Sequences</b>		
3-143-1	Sequence Number [ID]	143	
3-143-2	Molecule Type	AA	
3-143-3	Length	17	
3-143-4	Features Location/Qualifiers	<b>source 1..17</b> mol_type=protein organism=synthetic construct	
3-143-5	NonEnglishQualifier Value Residues	SITTGADHAI YADSVKG	17
<b>3-144</b>	<b>Sequences</b>		
3-144-1	Sequence Number [ID]	144	
3-144-2	Molecule Type	AA	
3-144-3	Length	32	
3-144-4	Features Location/Qualifiers	<b>source 1..32</b> mol_type=protein organism=synthetic construct	
3-144-5	NonEnglishQualifier Value Residues	RFTISRDNAL NTLYLQMNLS RAEDTAVYYC VR	32
<b>3-145</b>	<b>Sequences</b>		
3-145-1	Sequence Number [ID]	145	
3-145-2	Molecule Type	AA	
3-145-3	Length	12	
3-145-4	Features Location/Qualifiers	<b>source 1..12</b> mol_type=protein organism=synthetic construct	
3-145-5	NonEnglishQualifier Value Residues	HGYDGYHLF DY	12
<b>3-146</b>	<b>Sequences</b>		
3-146-1	Sequence Number [ID]	146	
3-146-2	Molecule Type	AA	
3-146-3	Length	11	
3-146-4	Features Location/Qualifiers	<b>source 1..11</b> mol_type=protein organism=synthetic construct	
3-146-5	NonEnglishQualifier Value Residues	WGQGLVTVS S	11