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(54) **CHIMERIC ANTIGEN RECEPTORS AND USES THEREOF**

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(58) **Field of Classification Search**

None  
See application file for complete search history.

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(57) **ABSTRACT**

The invention provides immune effector cells (for example, T cells, NK cells) that express a chimeric antigen receptor (CAR), and compositions and methods thereof.

**21 Claims, 55 Drawing Sheets**

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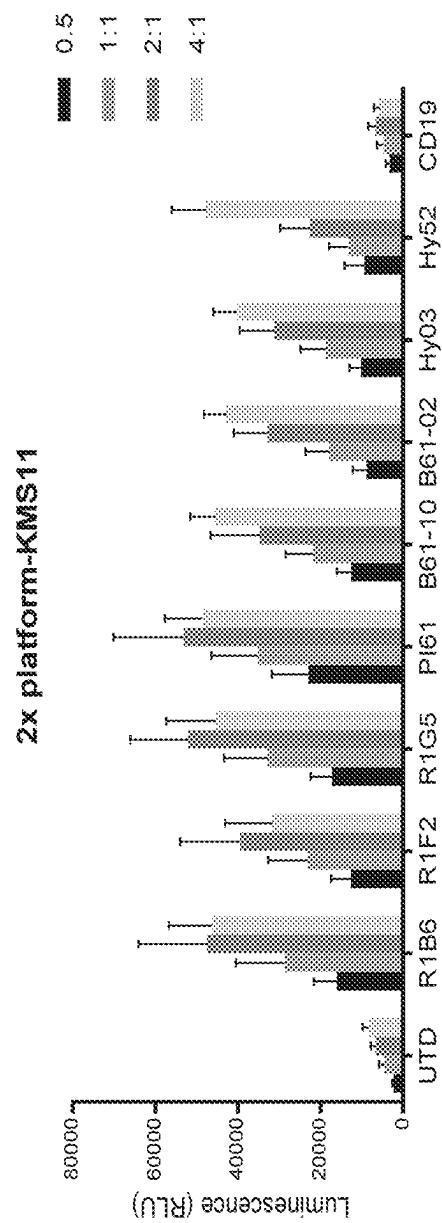
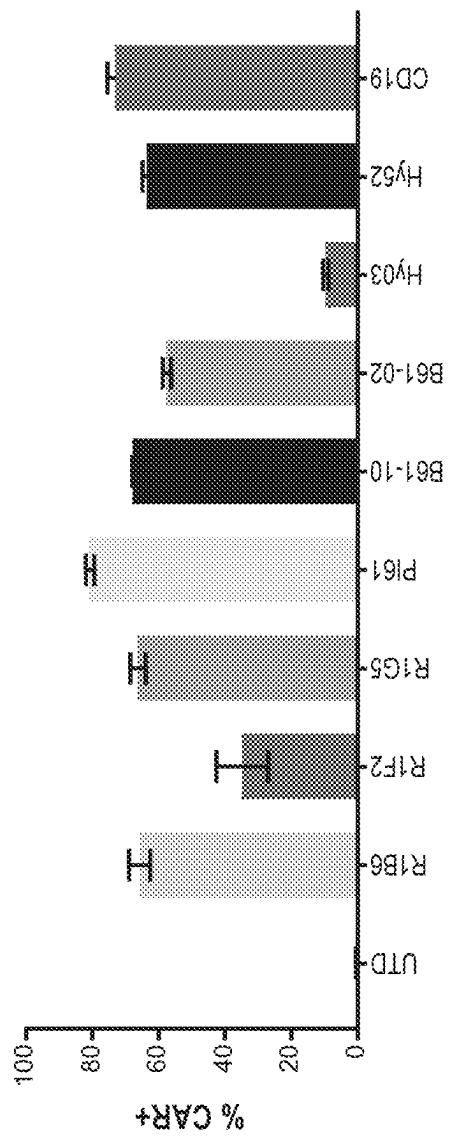


FIG. 1A



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FIG. 1C  
1xplatform-KMS11

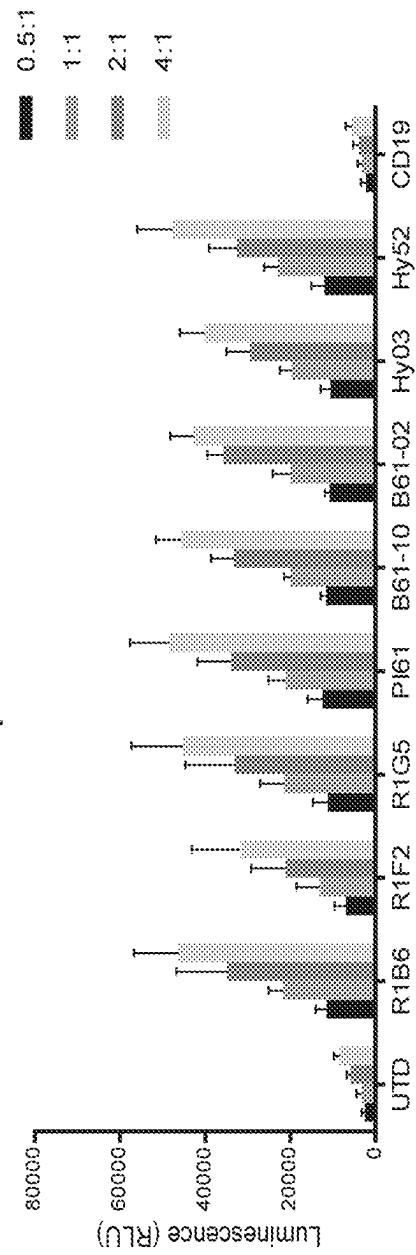


FIG. 1D  
CAR% (1x platform)

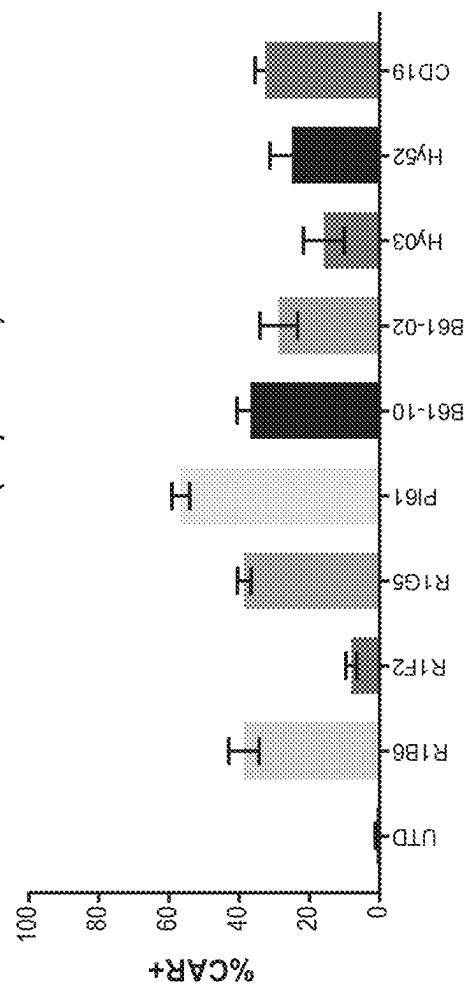


FIG. 1E

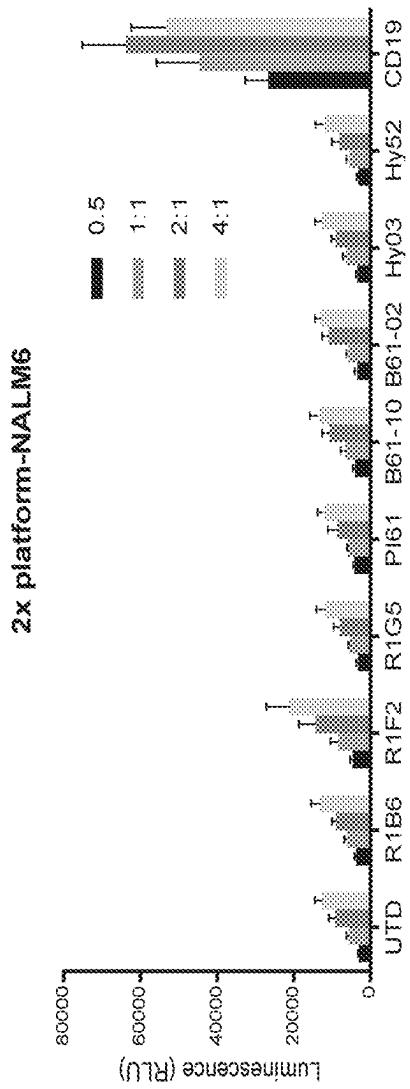


FIG. 1F

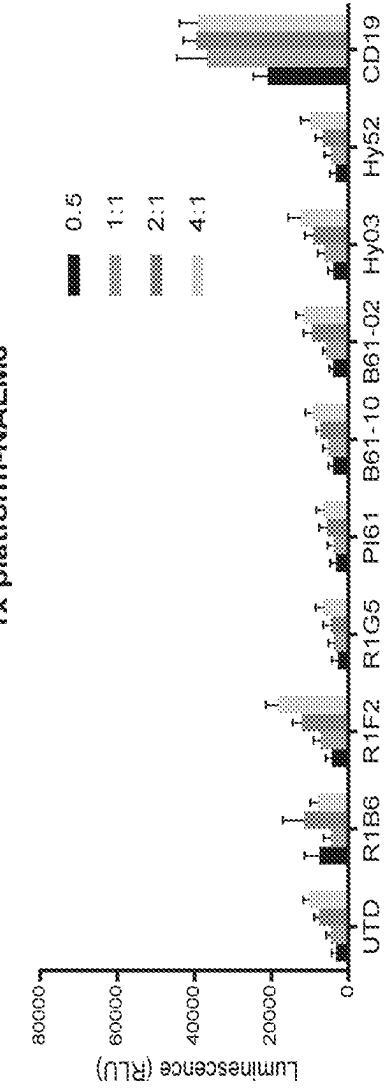


FIG. 1G

2x platform-media

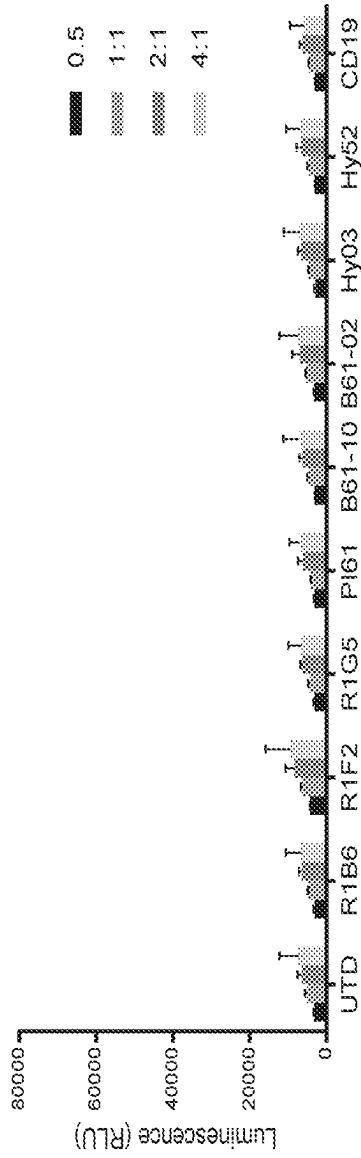


FIG. 1H

1x platform-media

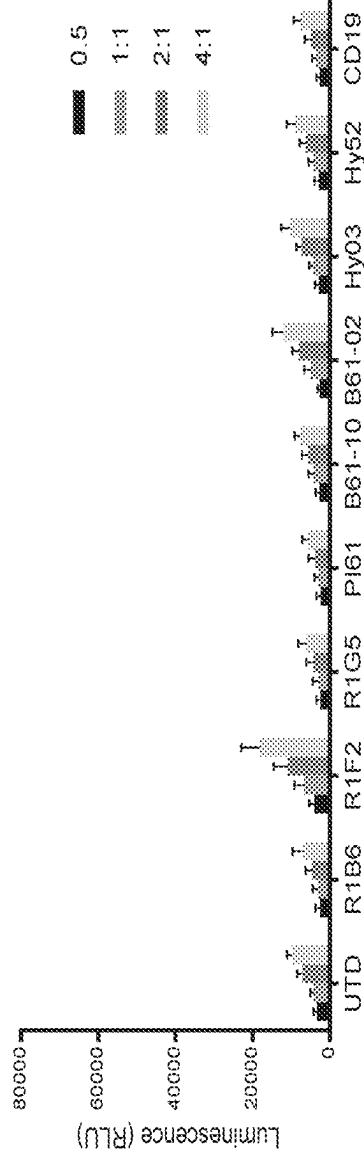
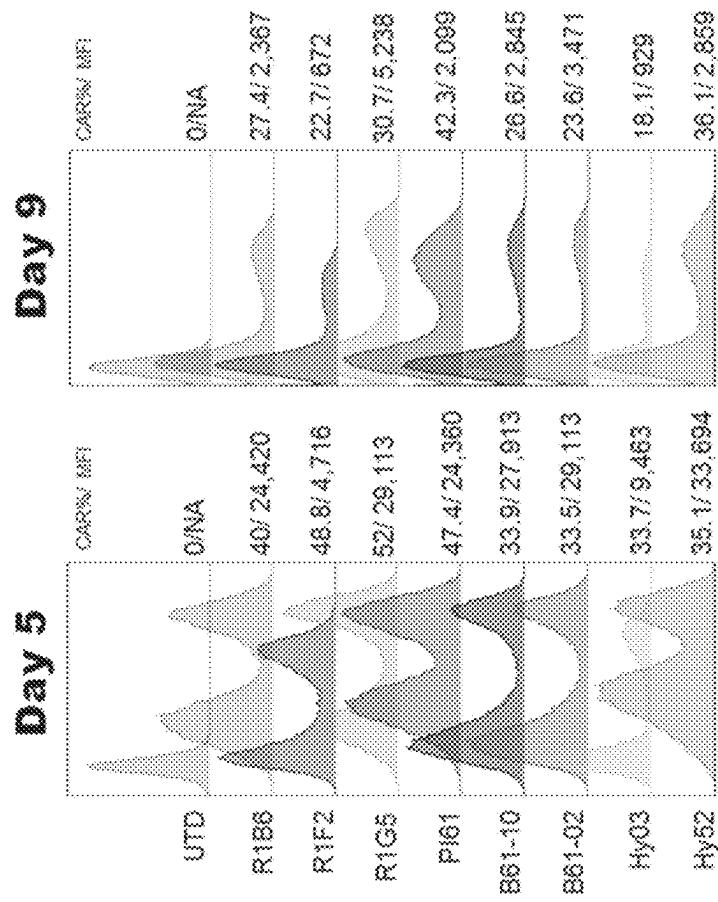
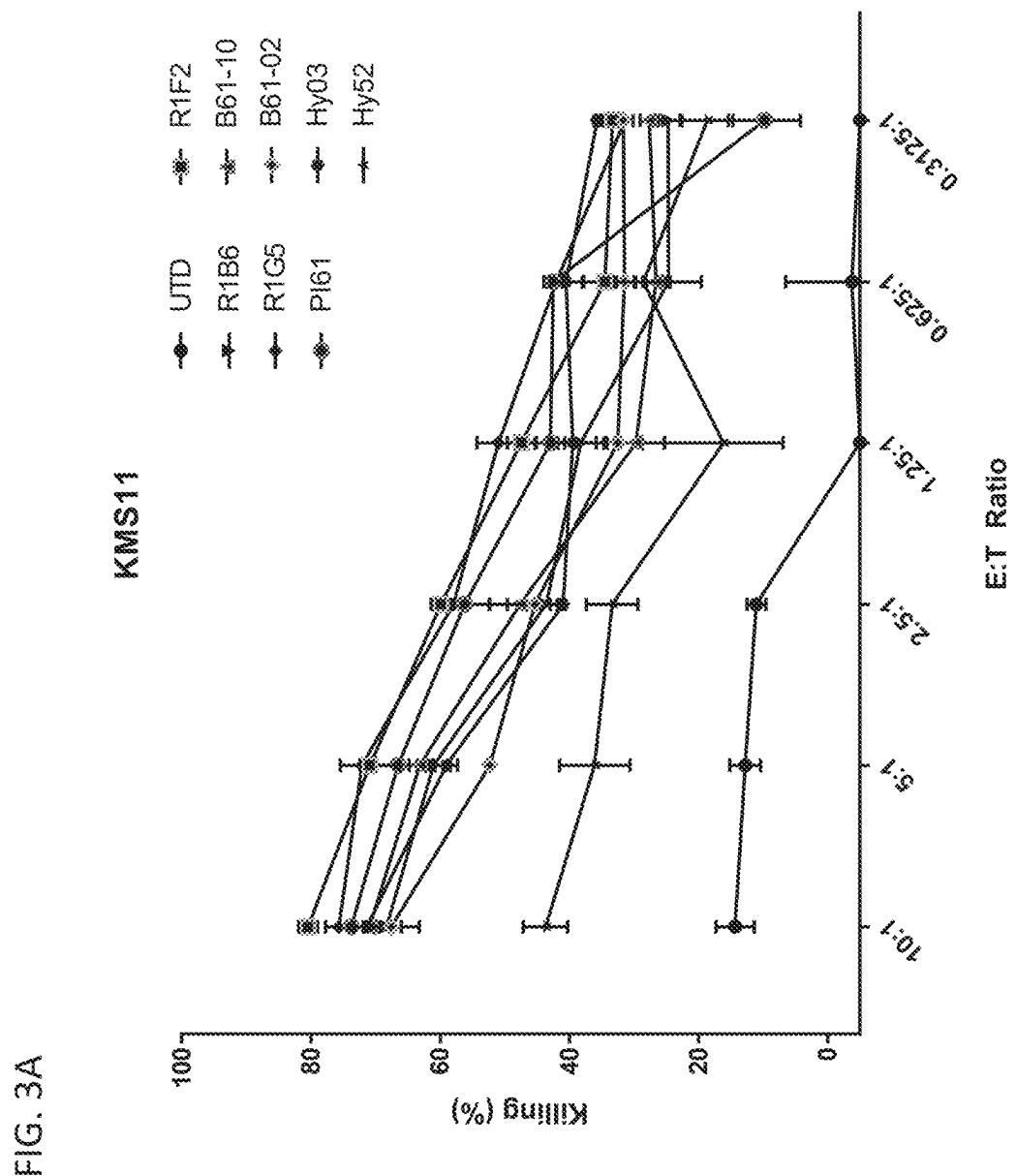
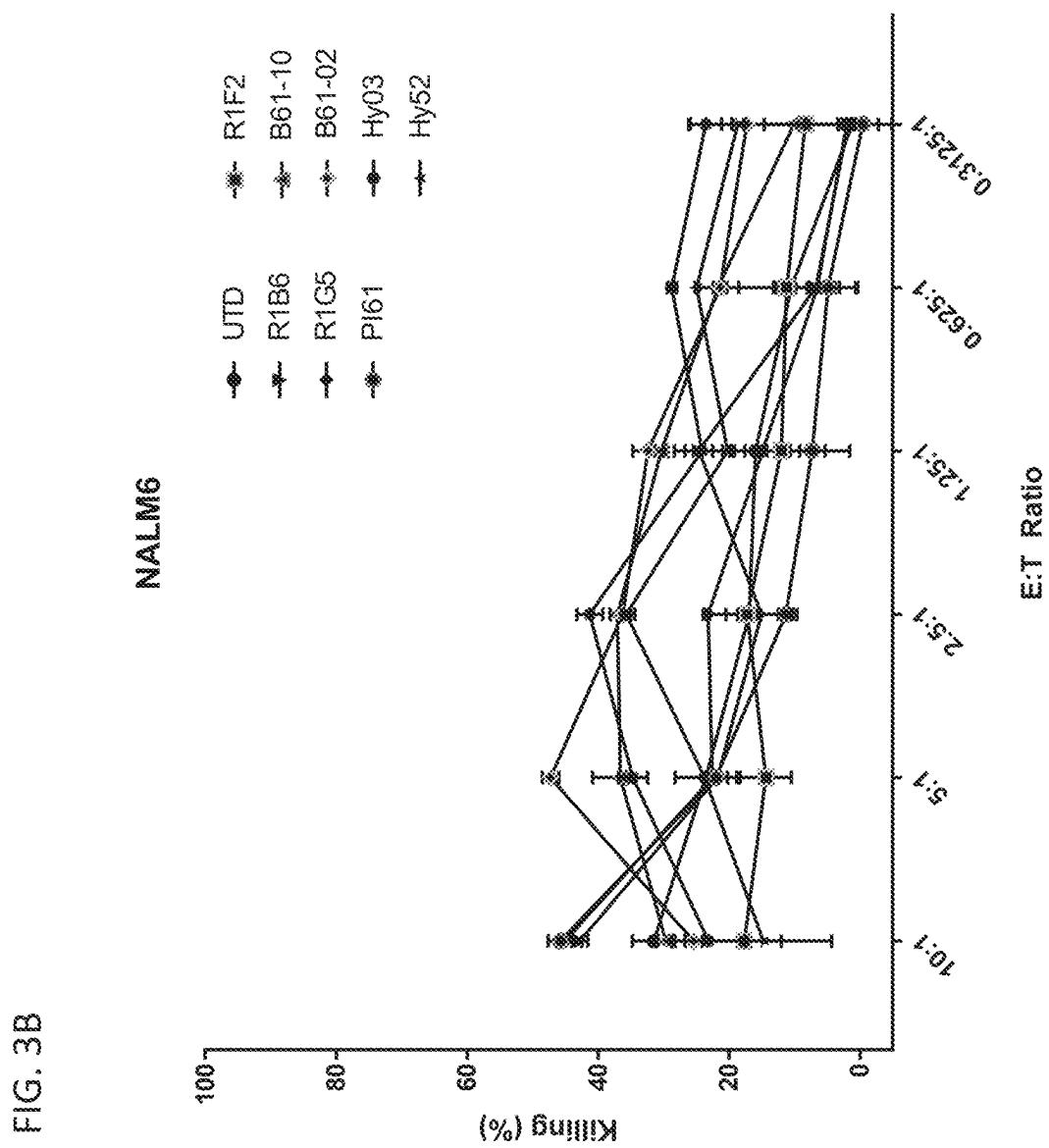


FIG. 2







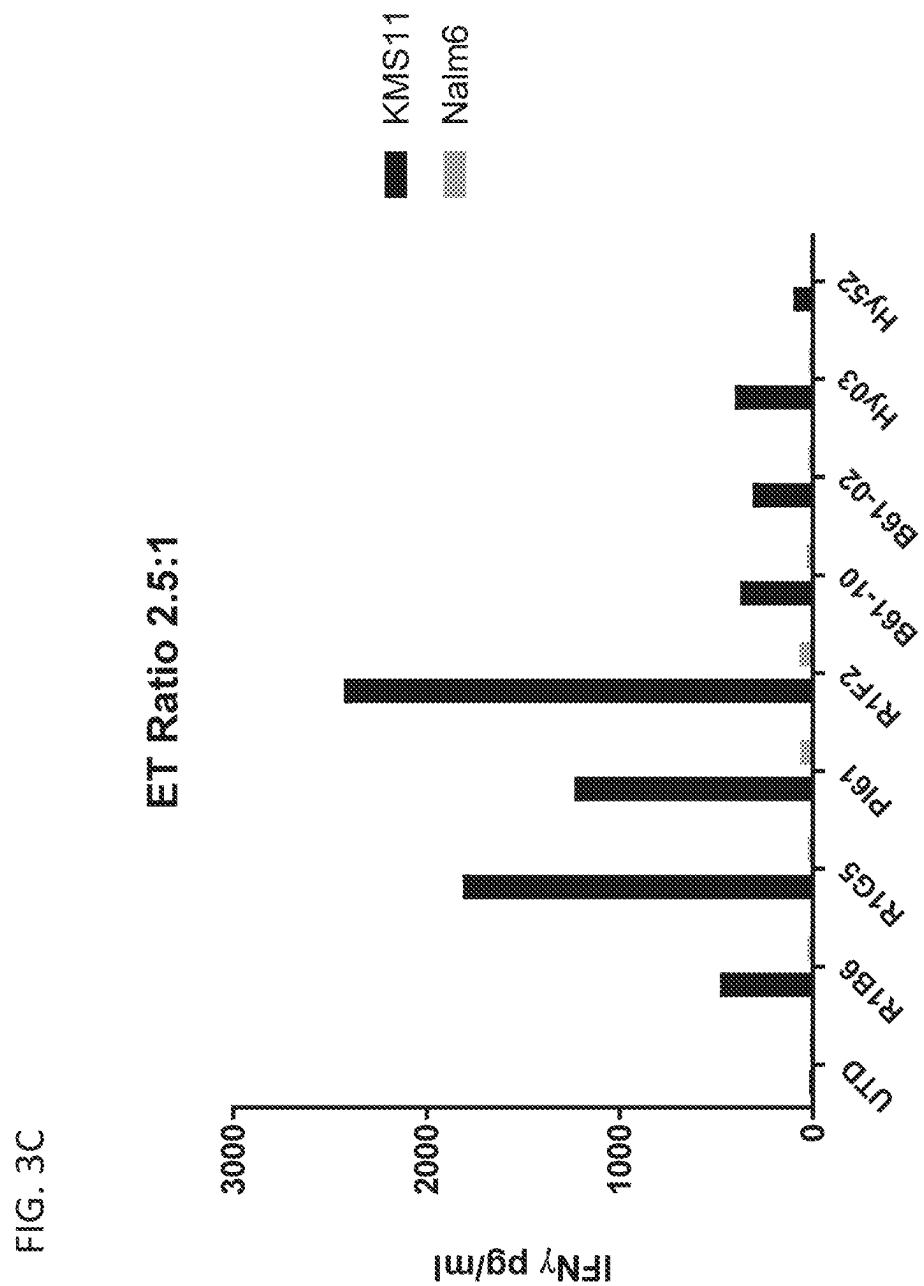


FIG. 4A

constructs	%CD19 CAR	%BCMA CAR	%Double Positive	CD19 CAR Only	BCMA CAR Only
UTD	0.01	0.01	0.00	0.01	0.01
234	7.43	3.47	3.73	3.62	0.06
235	1.35	1.35	1.21	0.13	0.18
236	10.10	10.30	9.62	0.35	0.77
237	10.40	9.61	9.31	0.96	0.59
238	12.10	9.89	9.74	2.12	0.47
244	31.60	0.04	0.04	31.40	0.01

FIG. 4B

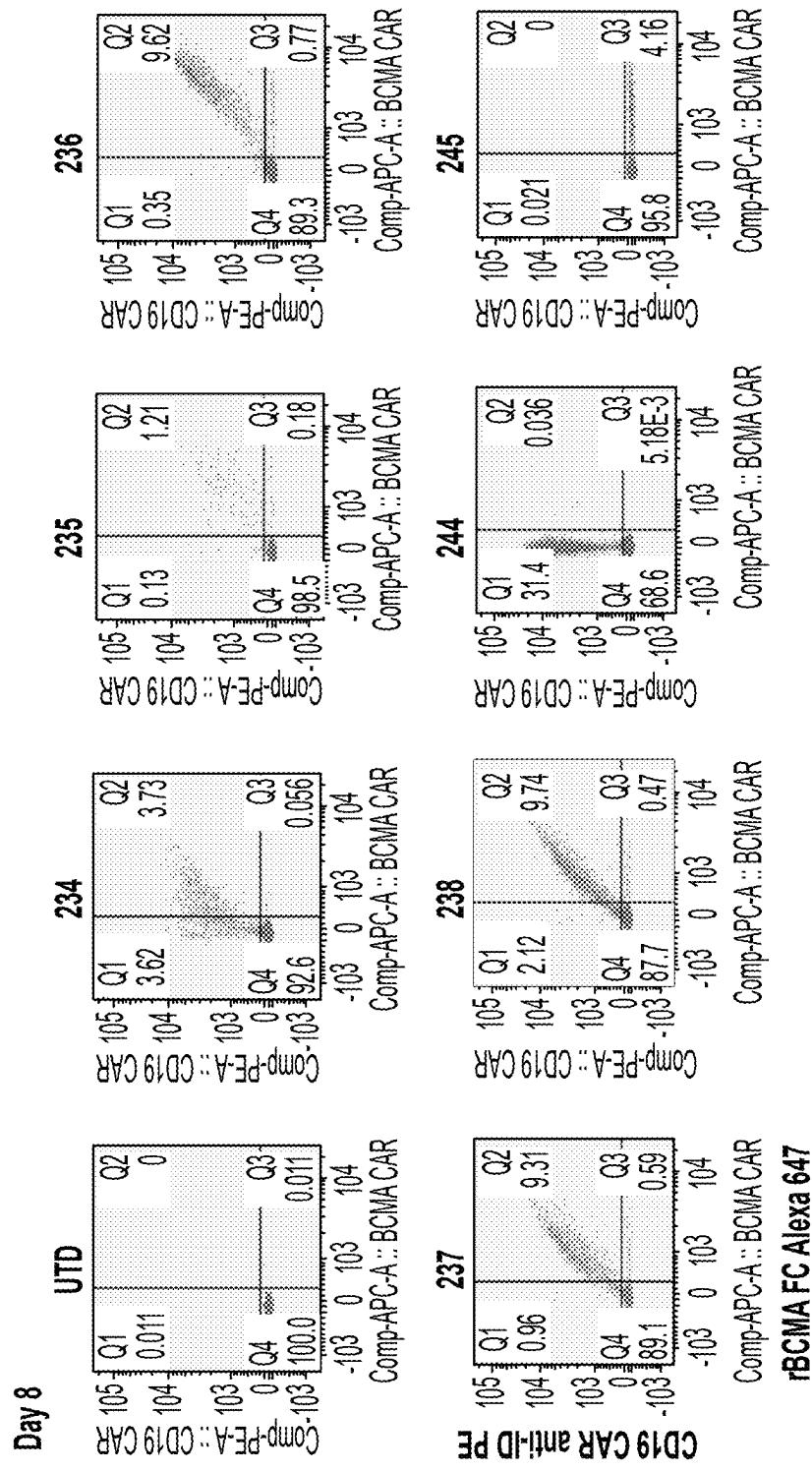


FIG. 4C

BCMA CAR and CD19 CAR MFI per CART on day 8

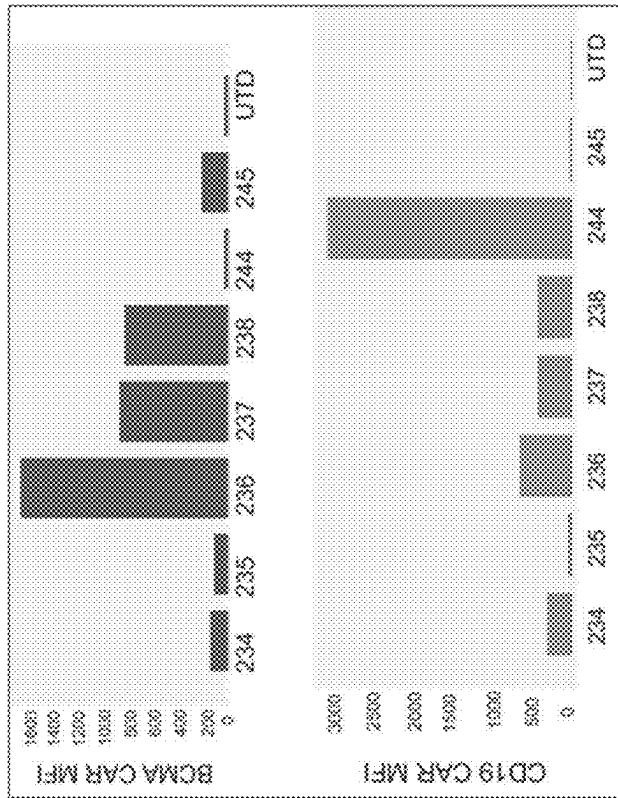


FIG. 5A

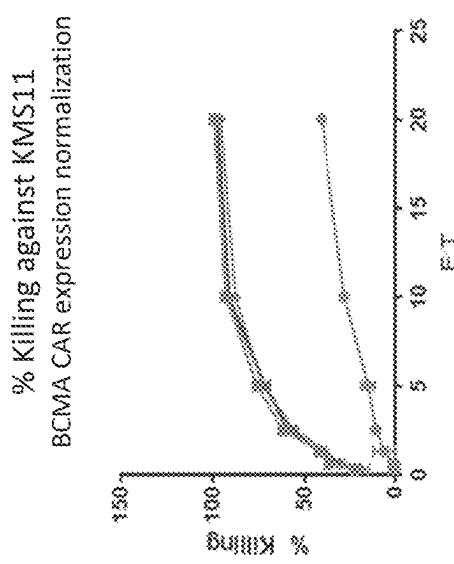


FIG. 5B

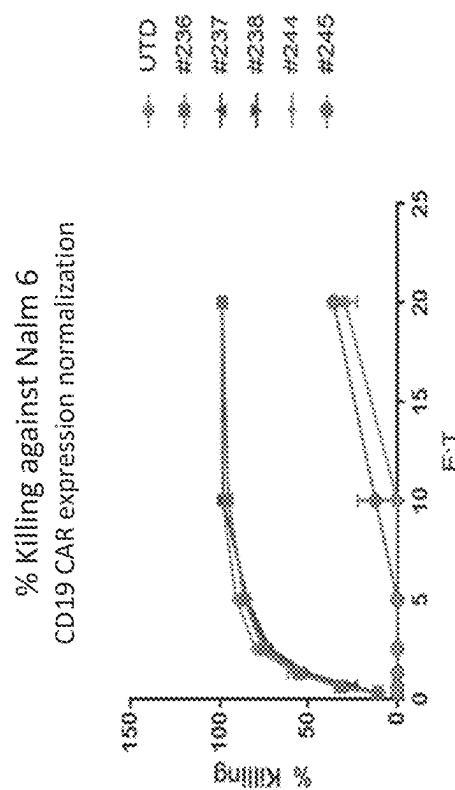
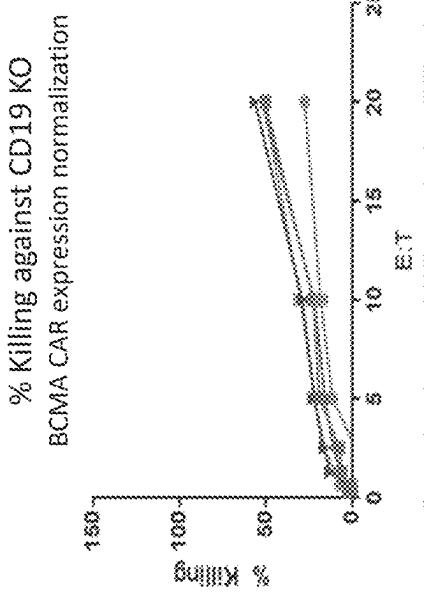


FIG. 5C



% Killing against CD19 KO BCMA CAR expression normalization

--- UTD  
--- #236  
--- #237  
--- #238  
--- #245  
--- #244

--- UTD  
--- #236  
--- #237  
--- #238  
--- #245  
--- #244

--- UTD  
--- #236  
--- #237  
--- #238  
--- #245  
--- #244

FIG. 6A

## CD19 CAR normalization

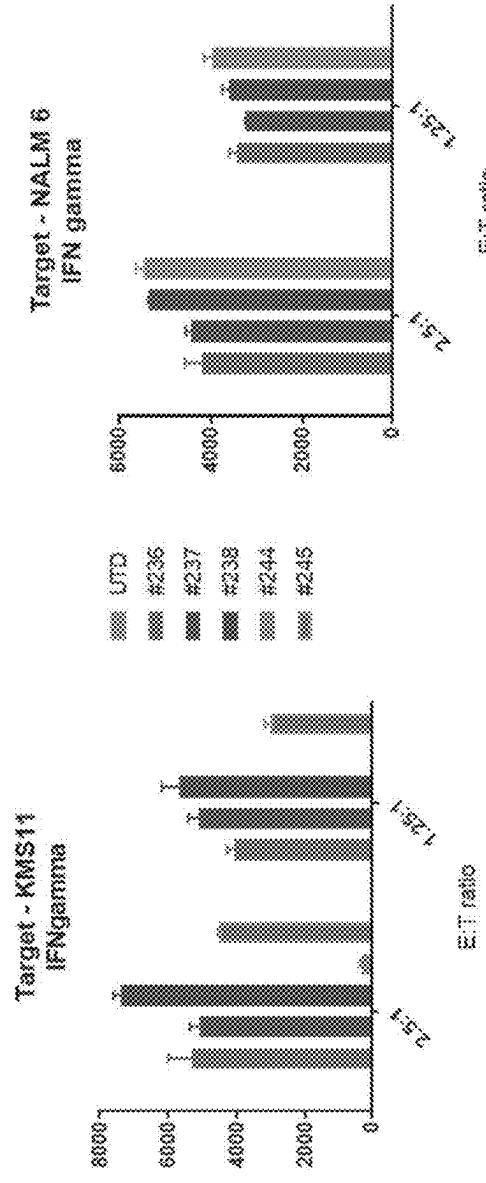


FIG. 6B

## CD19 CAR normalization

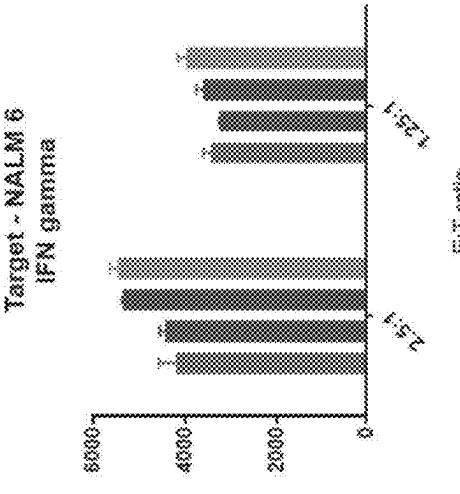


FIG. 6C

## BCMA CAR normalization

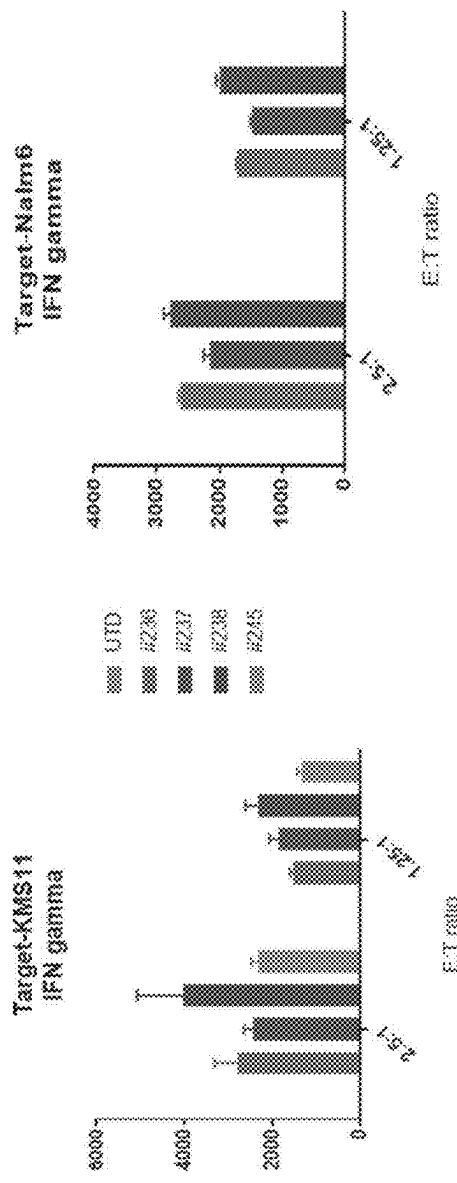


FIG. 6D



FIG. 7A

**Day 1 Histograms of CAR T product using MoI=1 based on the upstream CAR titer**

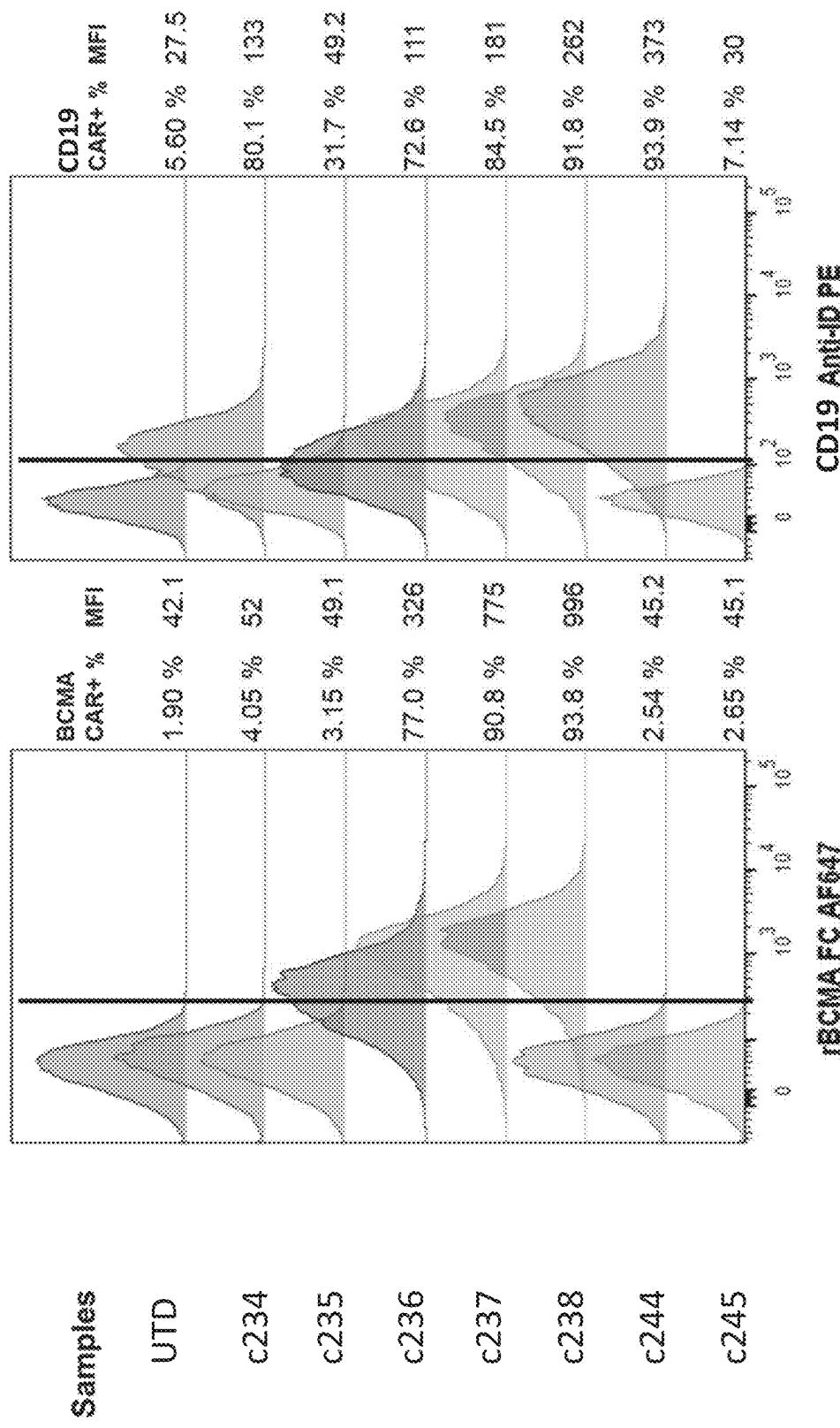


FIG. 7B

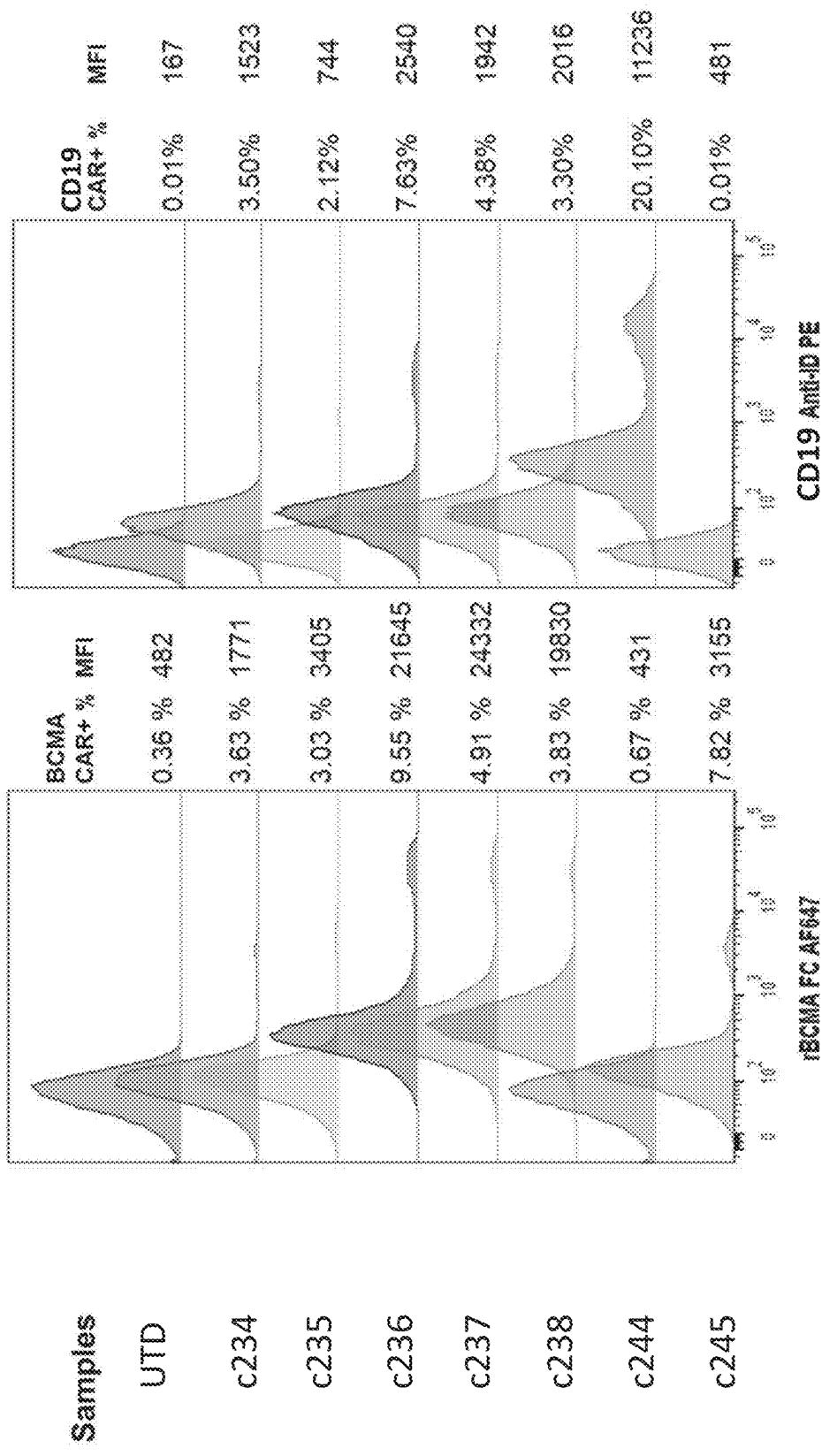
**Day 3 Histograms of CAR product using MOI=1 based on the upstream CAR titer**

FIG. 7C

Day 3 Plots (upstream CAR titer)

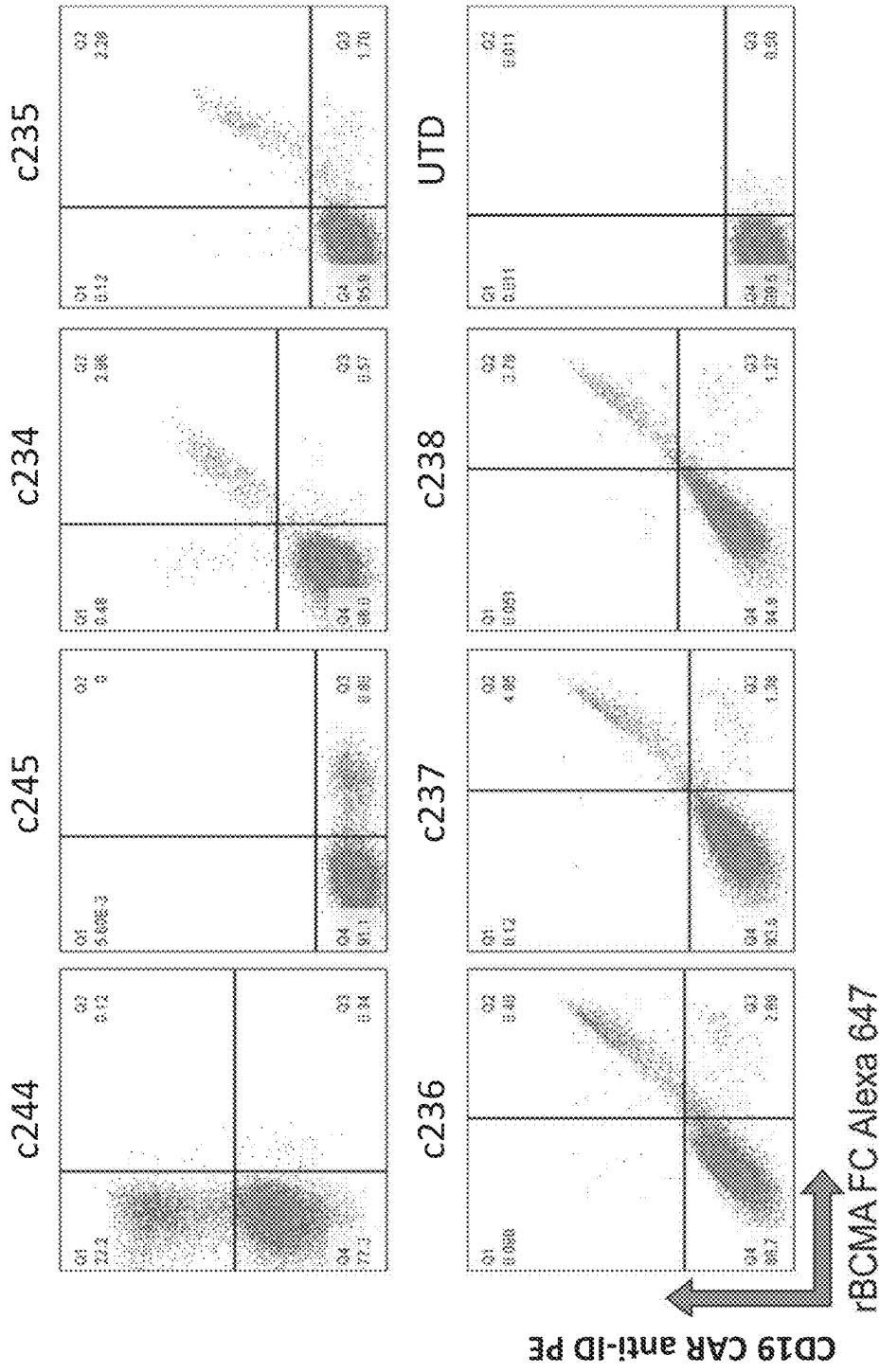


FIG. 8A

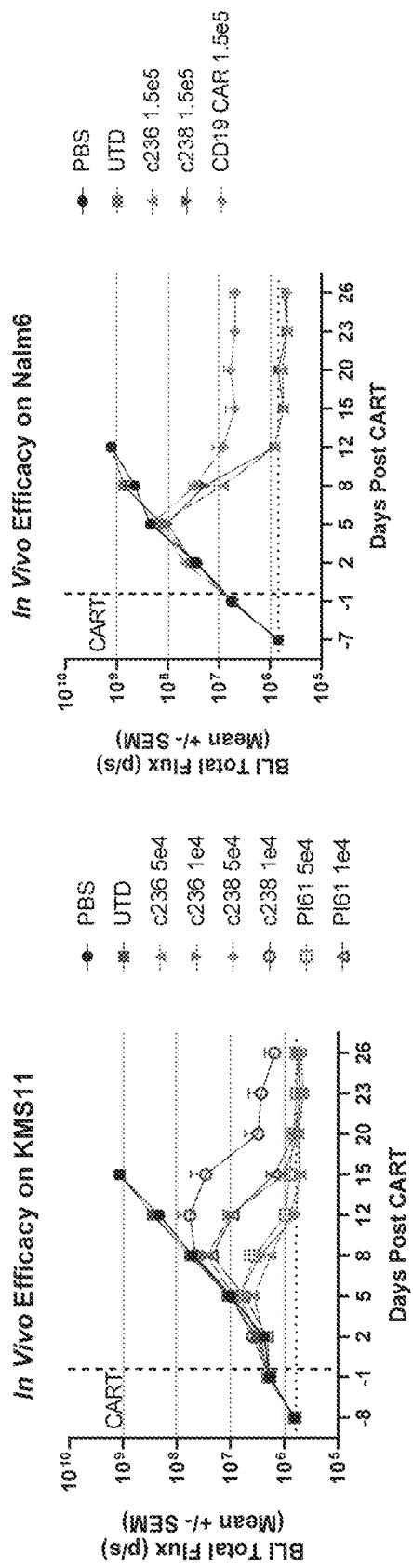


FIG. 8B

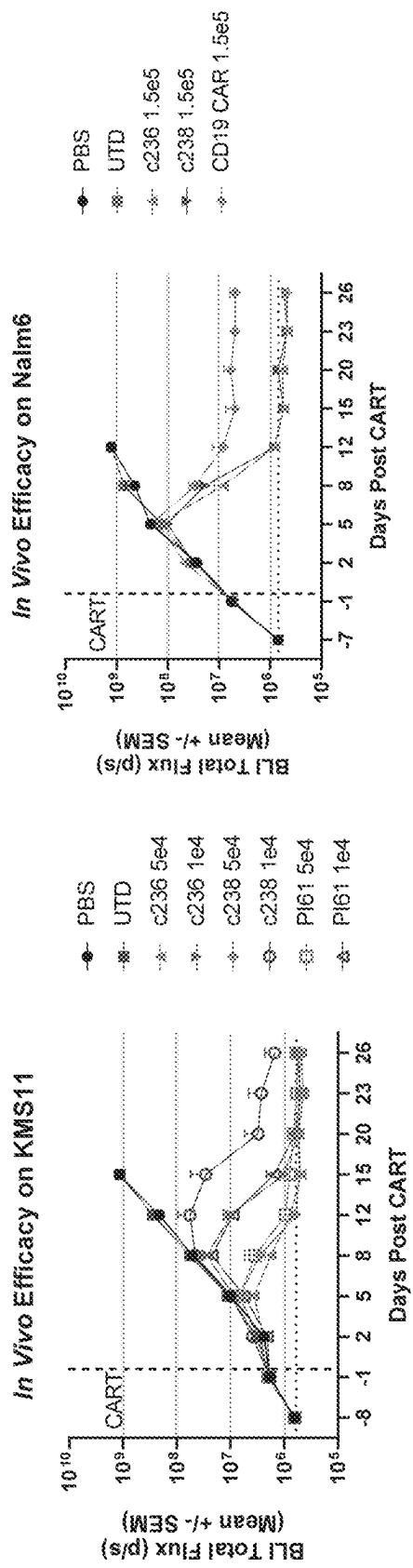


FIG. 8C

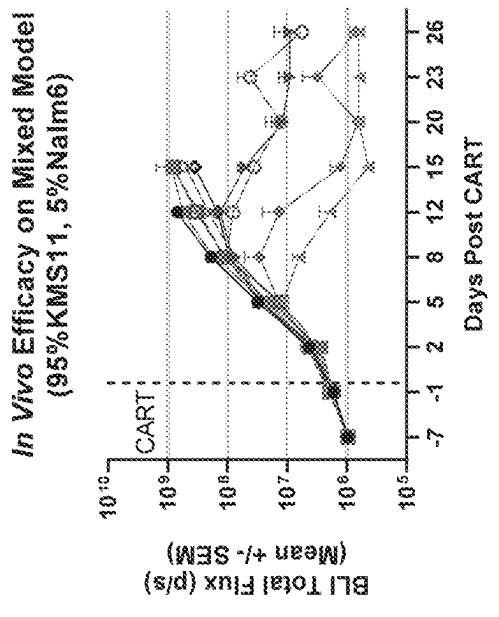


FIG. 9A

## KWS11 BW Change

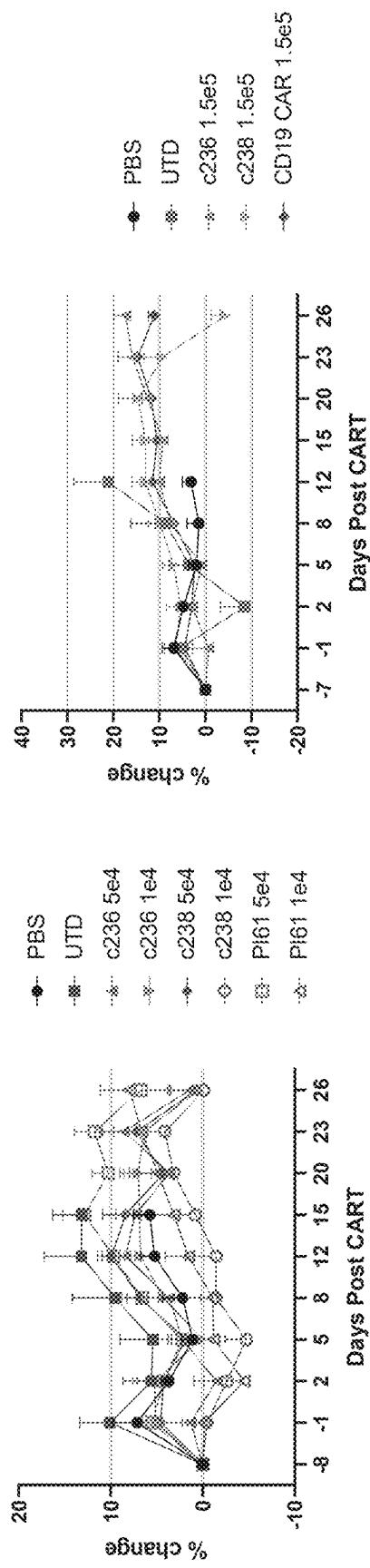


FIG. 9B

## Nalm6 BW Change

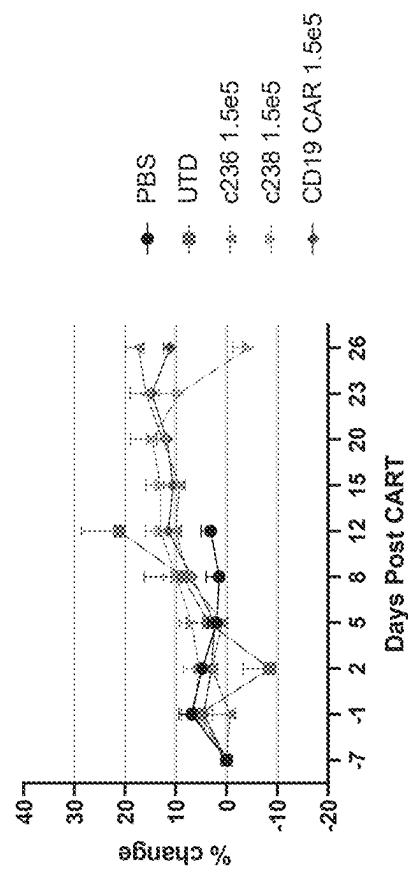


FIG. 9C

## Mixed Model BW Change

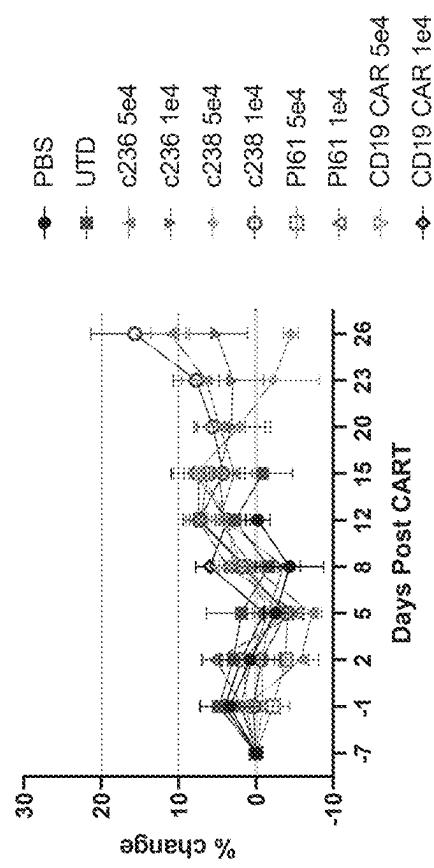


FIG. 10A

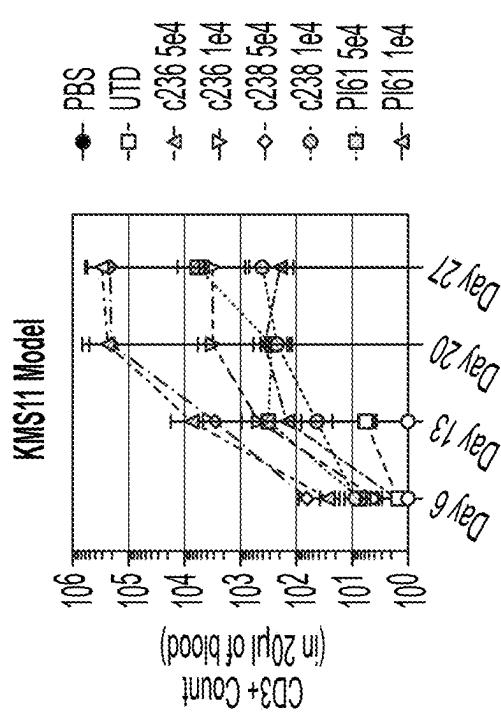
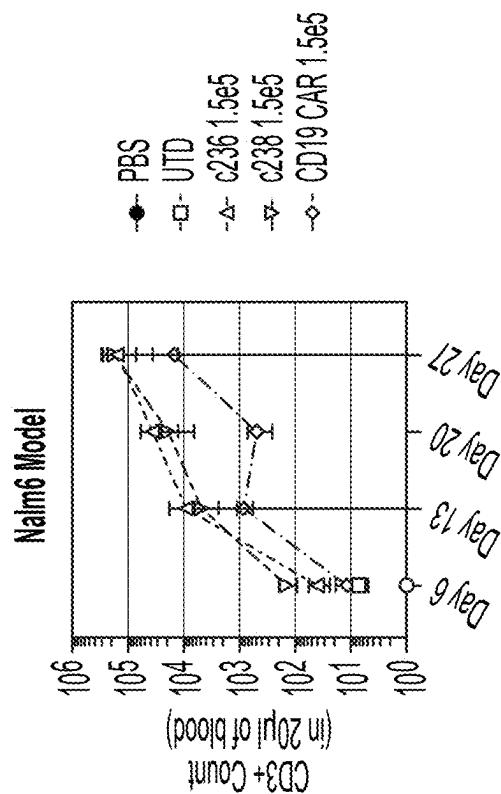


FIG. 10B



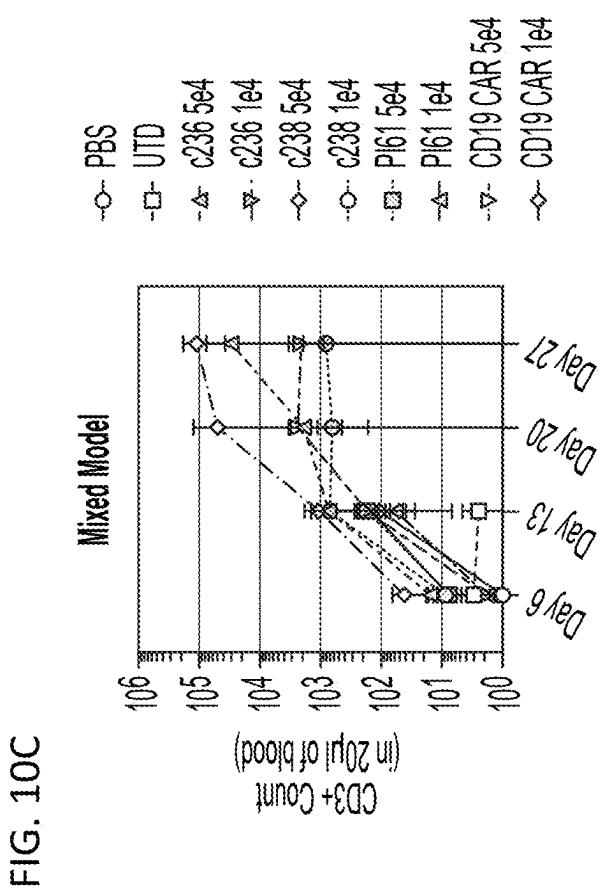


FIG. 11A

## KMS11 Model BCMA CAR+

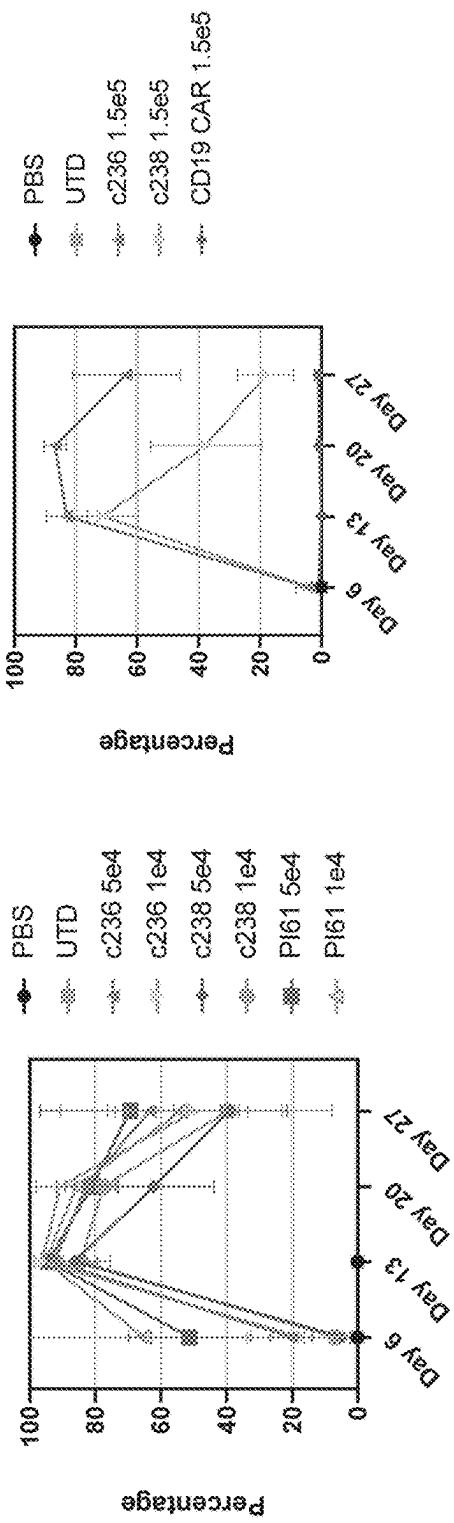


FIG. 11B

## Nalm6 Model BCMA CAR+

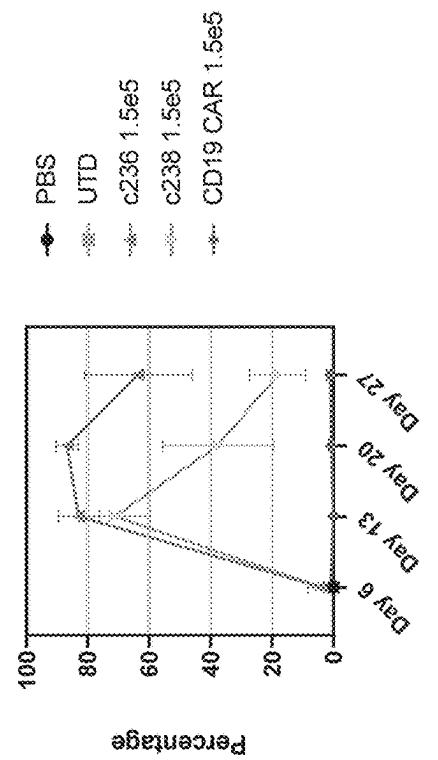


FIG. 11C

## Mixed Model BCMA CAR+

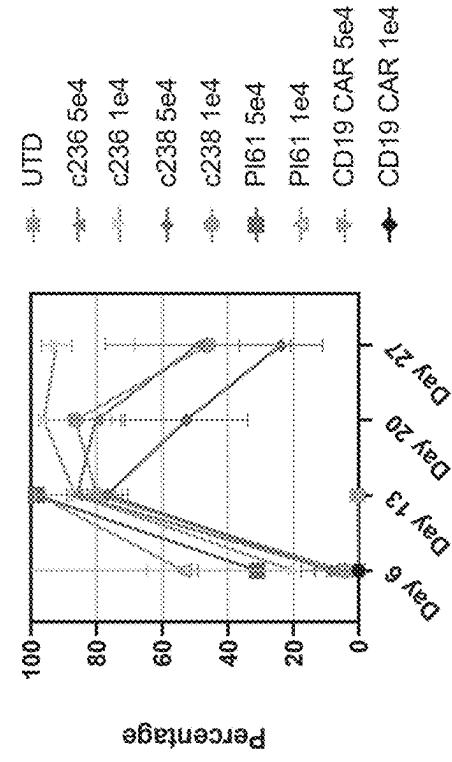
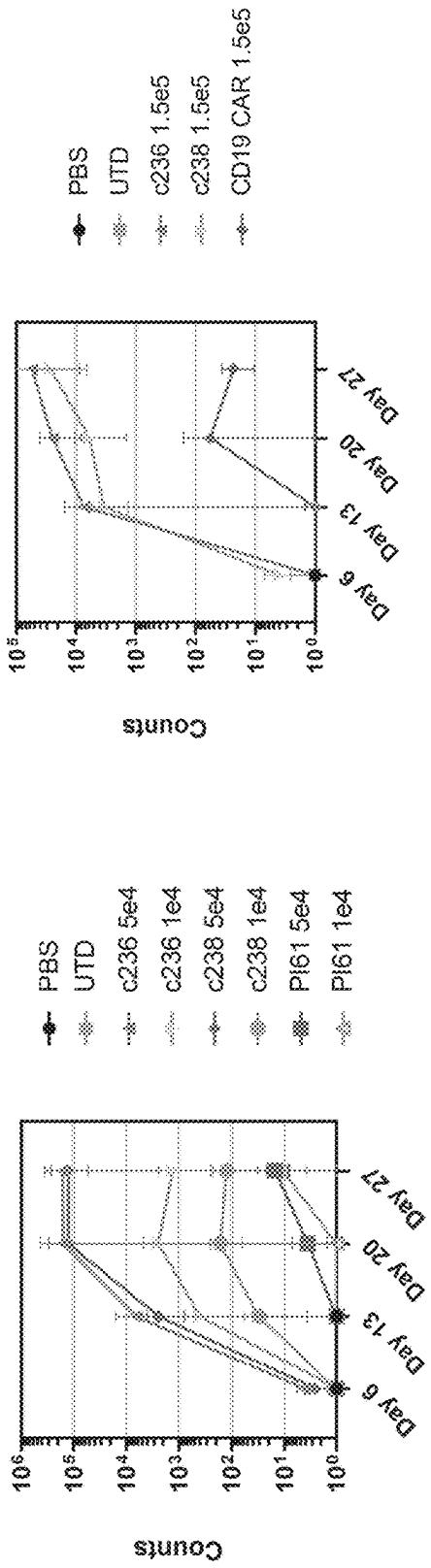


FIG. 12A

KMS11 Model Double CAR+



128

Nalm6 Model Double CAR+

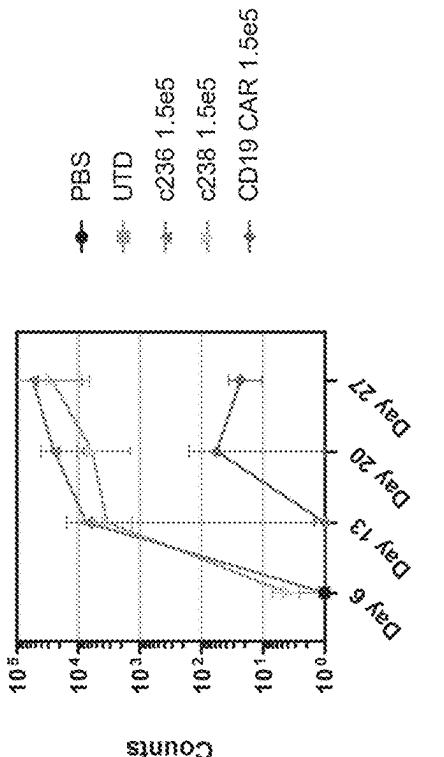


FIG. 12C

Mixed Model Double CAR+

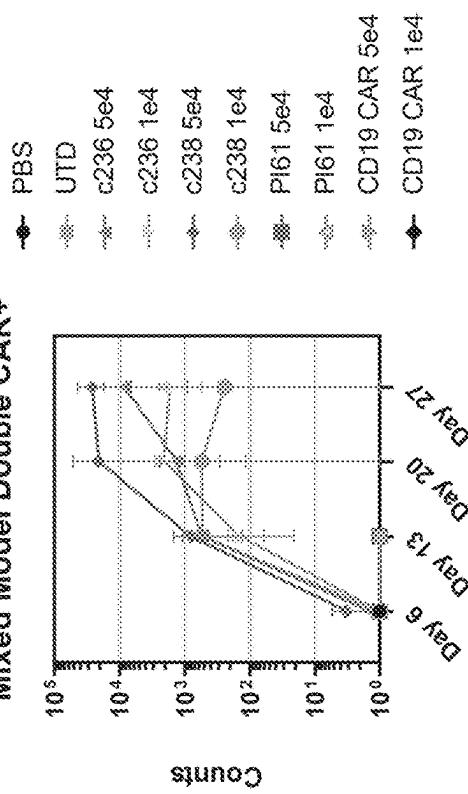


FIG. 13A

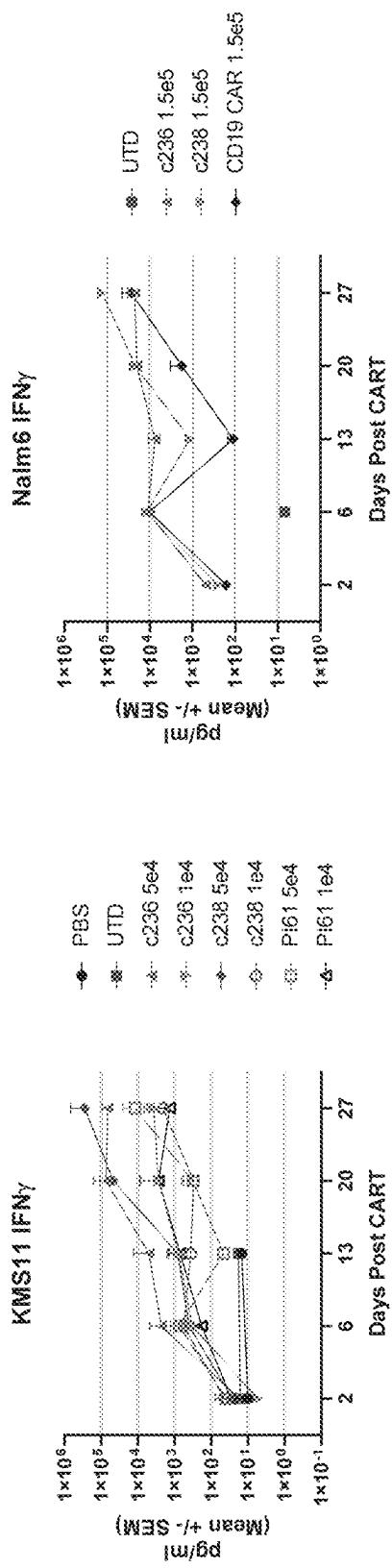


FIG. 13B

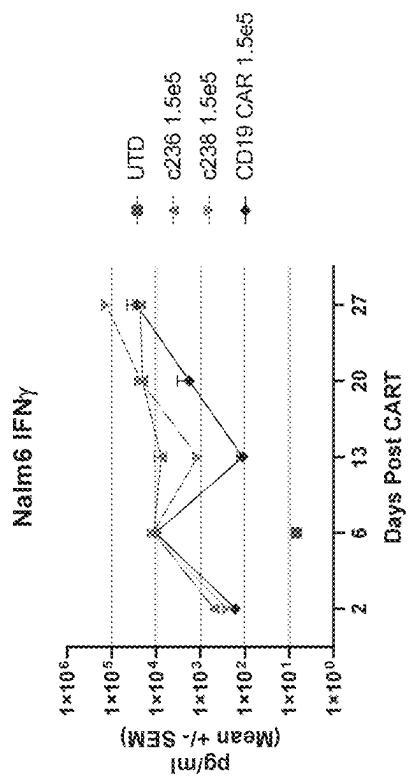


FIG. 13C

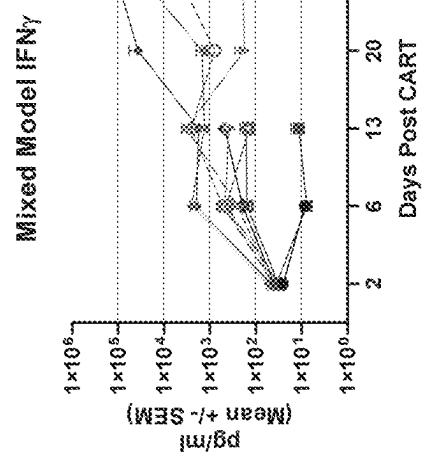


FIG. 14A In vivo efficacy in a multiple myeloma model

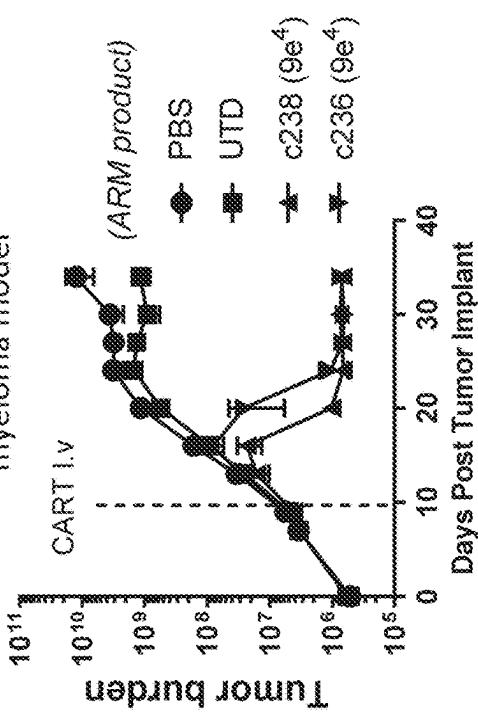
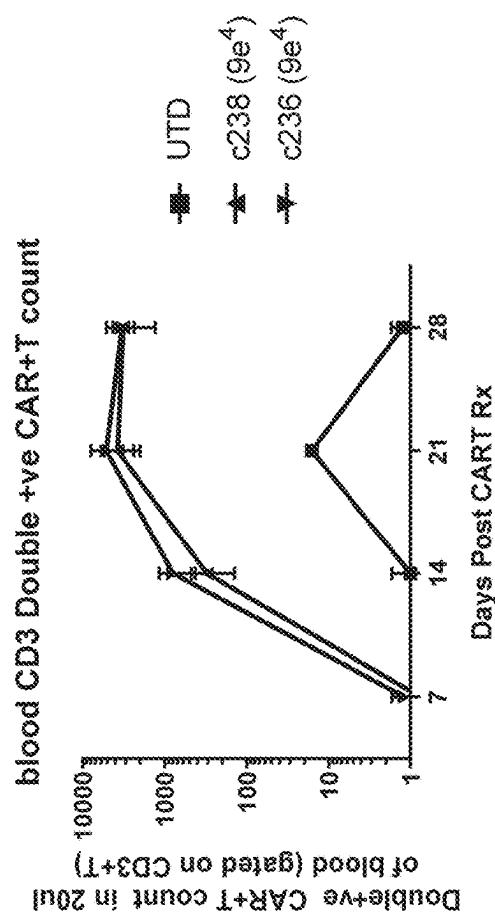
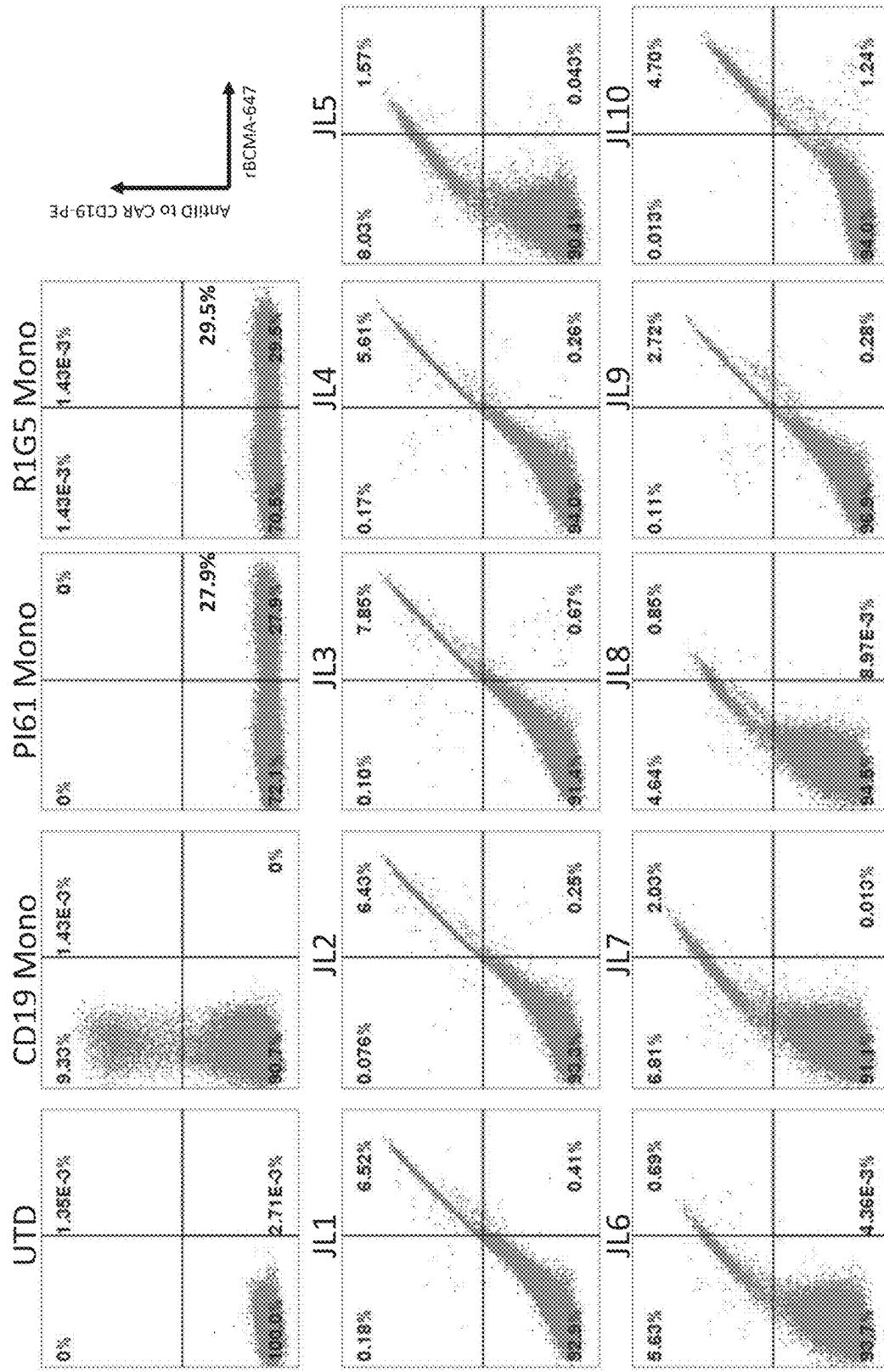


FIG. 14B



CAR expression 96h post viral addition with ARM process (MOI=2)



CAR expression 7 days post viral addition with ARM process (MOI 2)

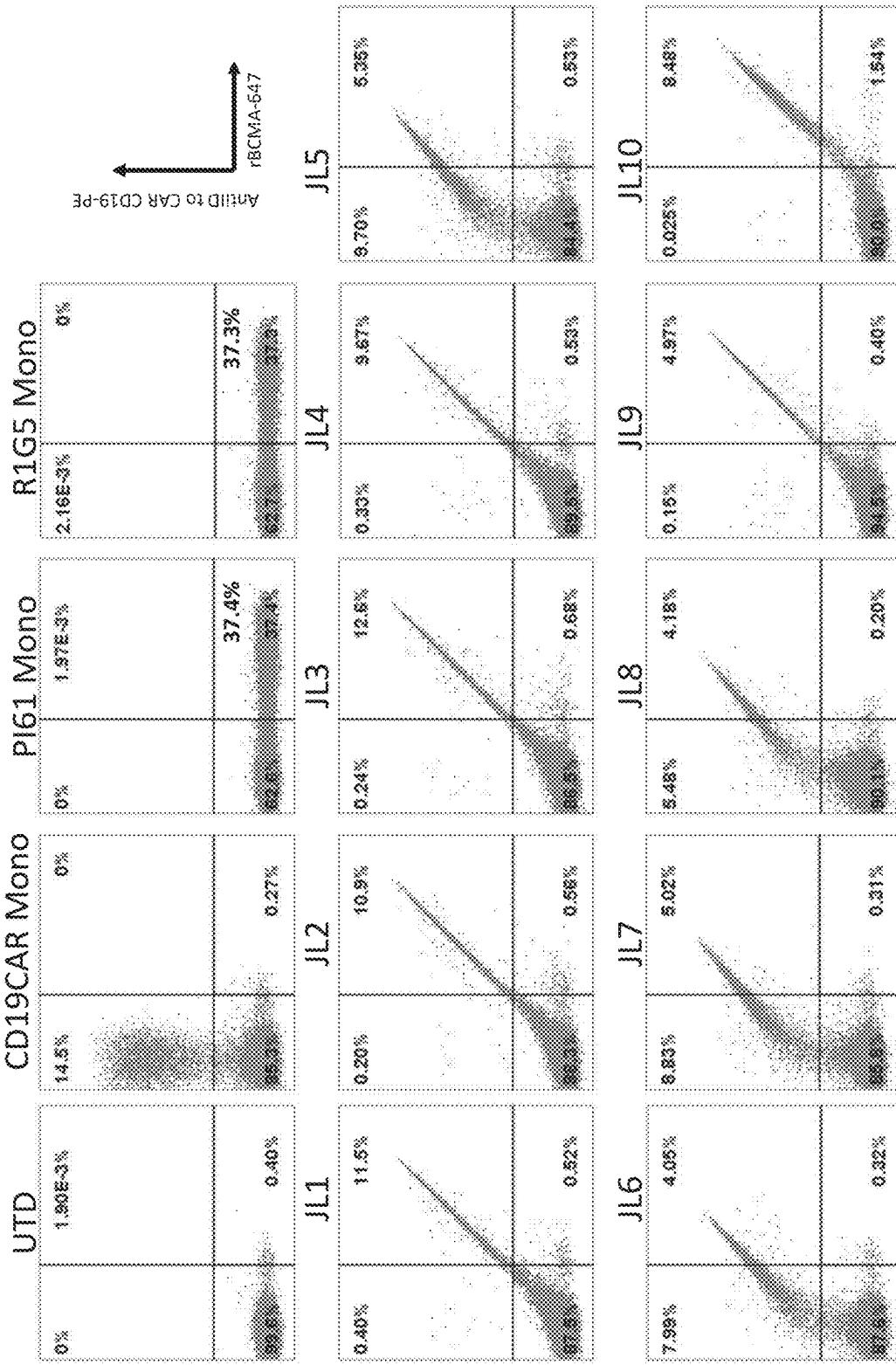


FIG. 16

## CAR Expression at day 7 with TM process (MOI 5)

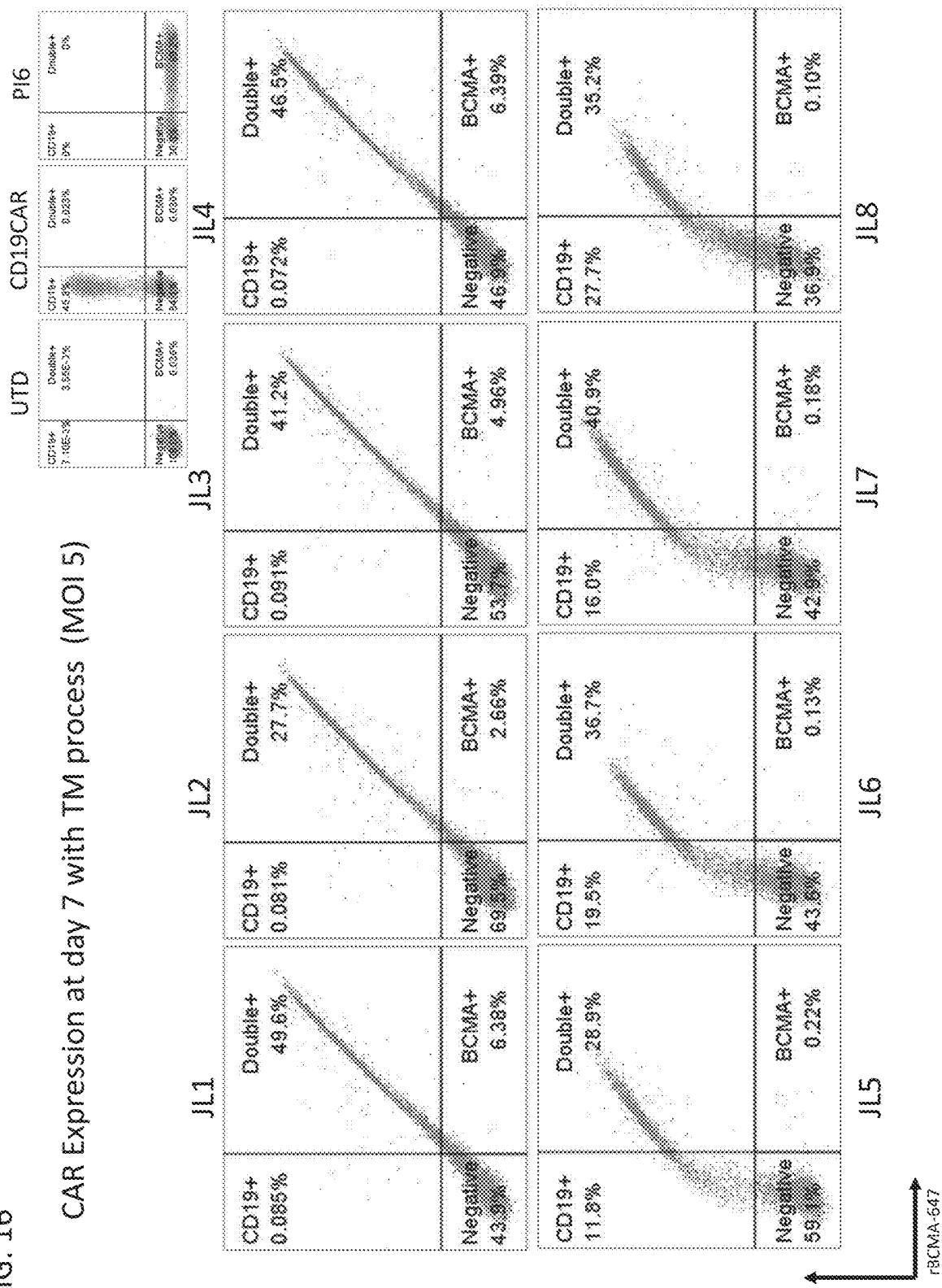


FIG. 17A  
FIG. 17B

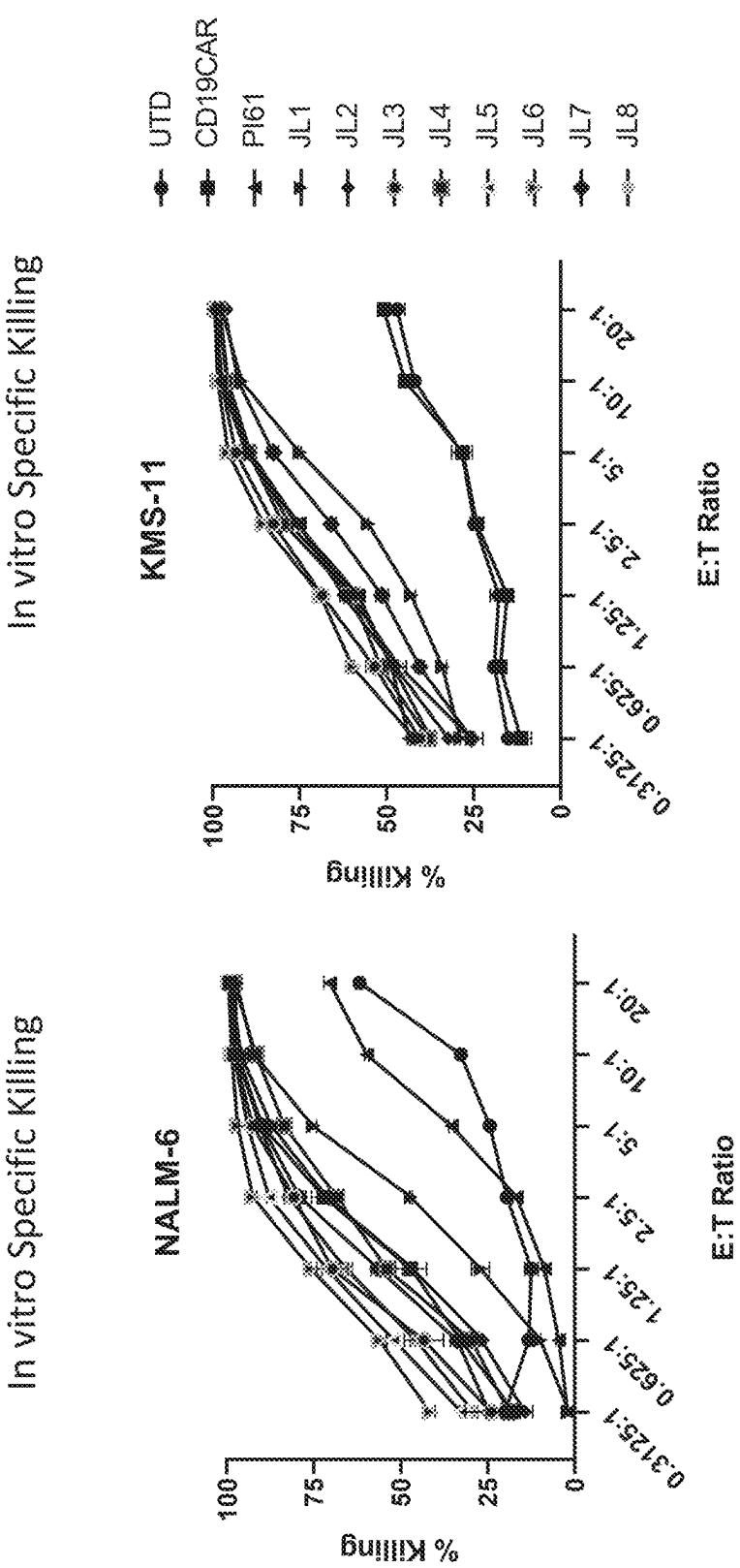


FIG. 18A

## Cytokine Release

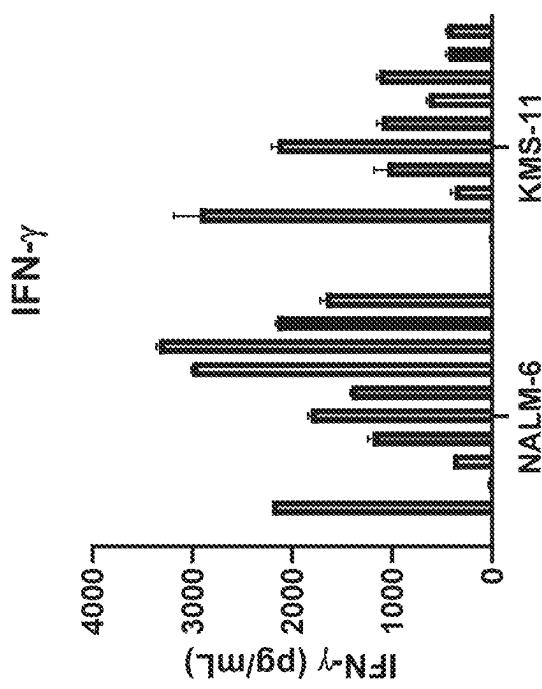
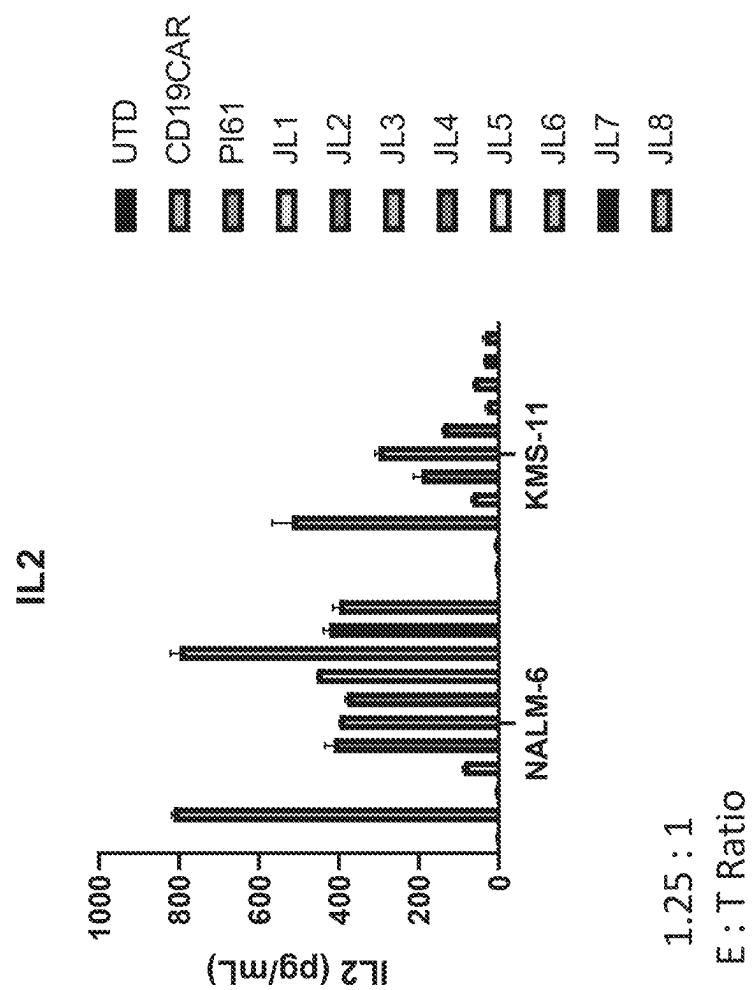


FIG. 18B

## Cytokine Release



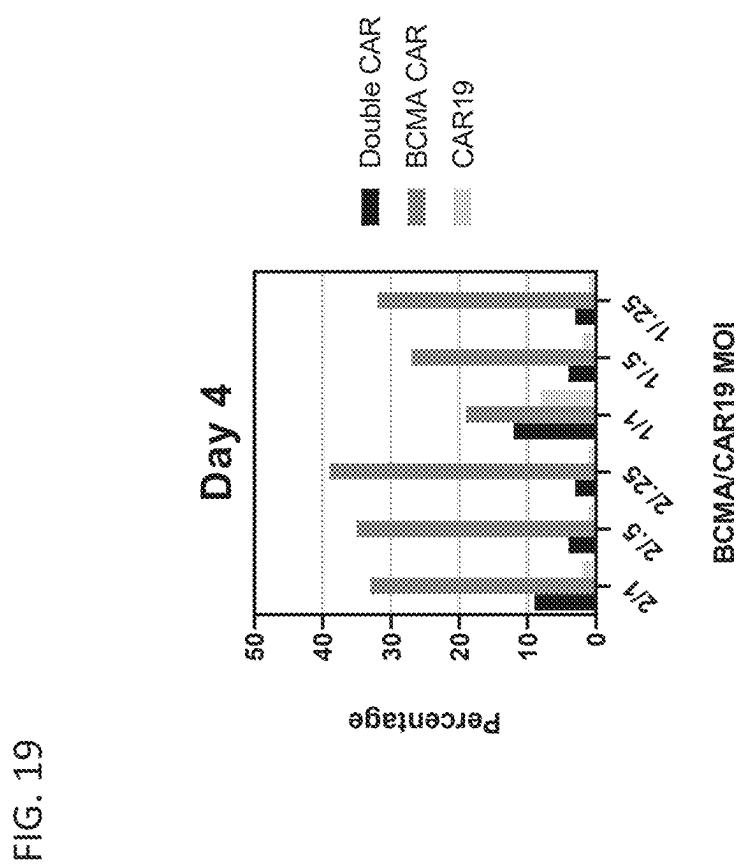
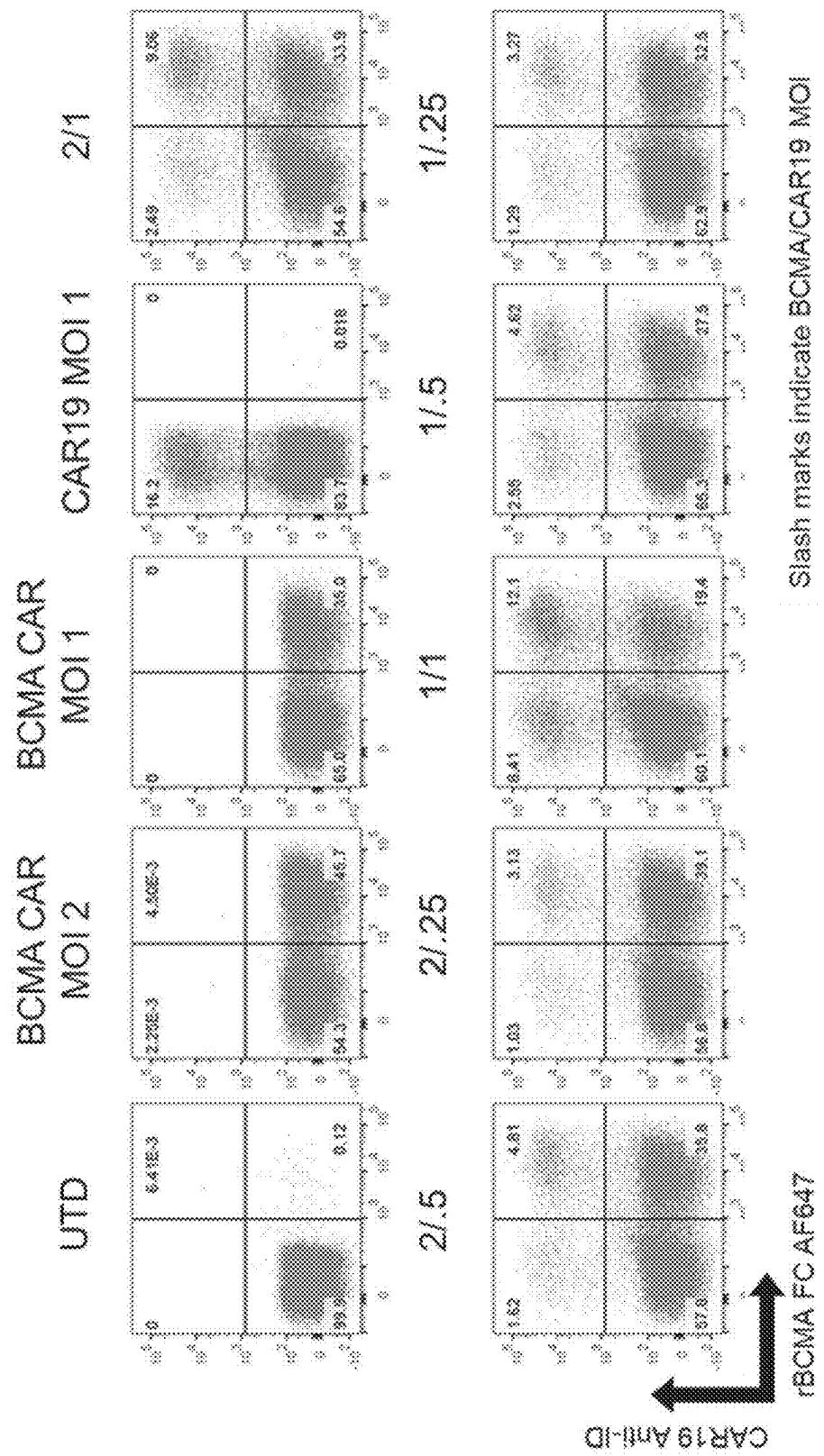


FIG. 20



EIG. 21

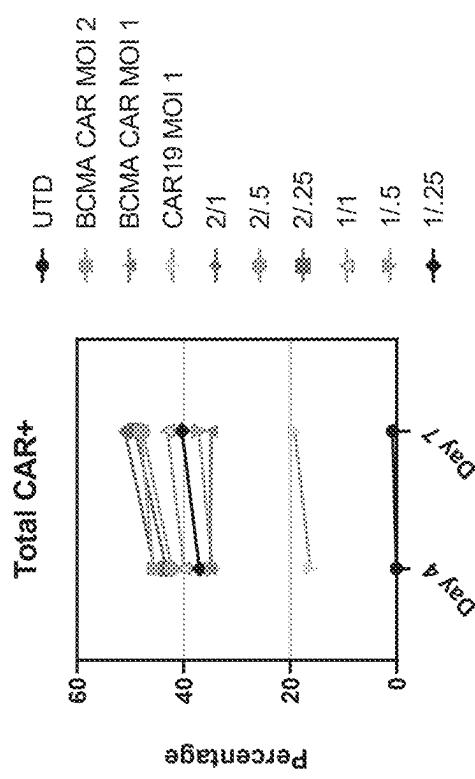


FIG. 22

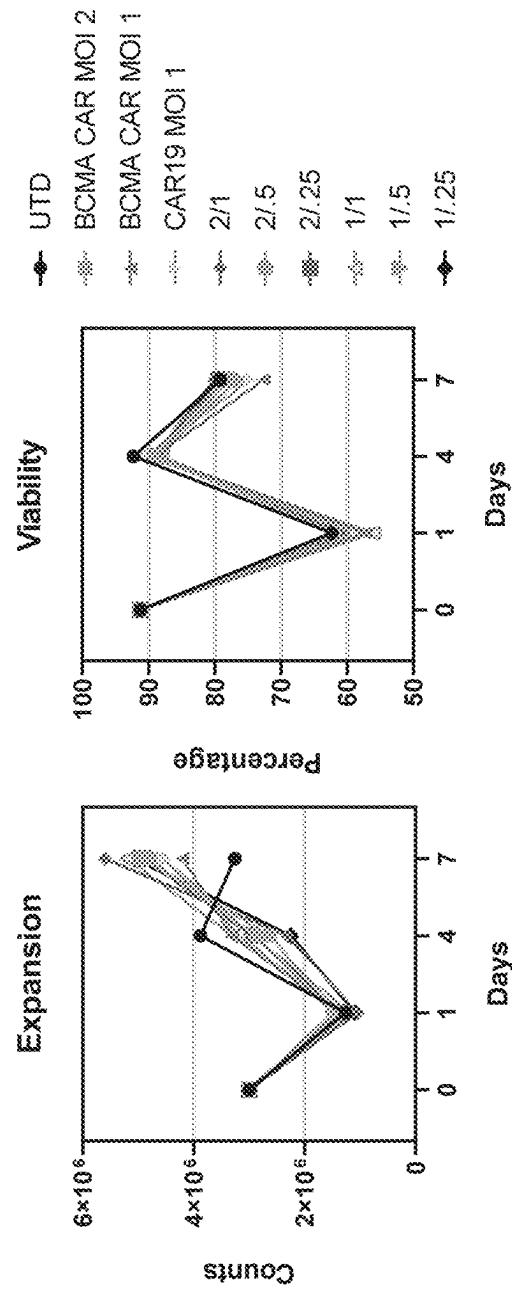


FIG. 23A

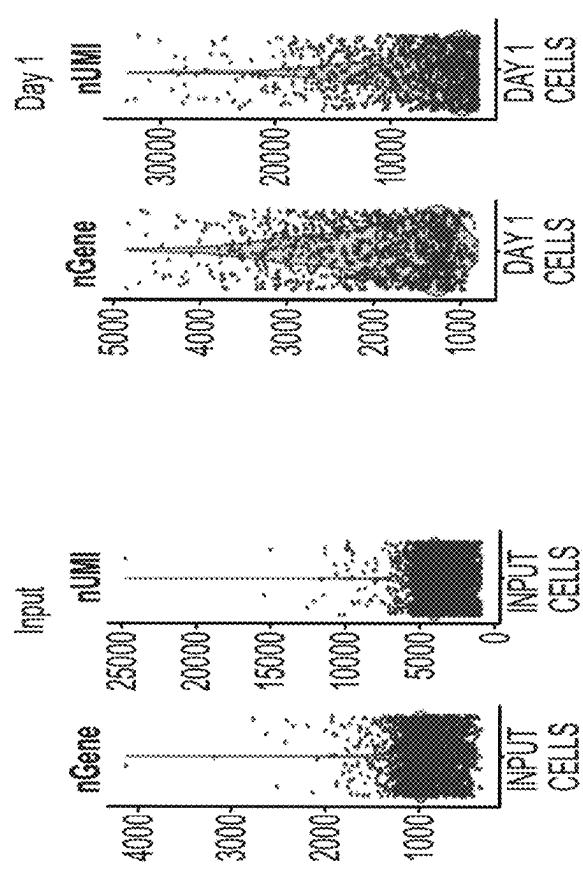


FIG. 23B

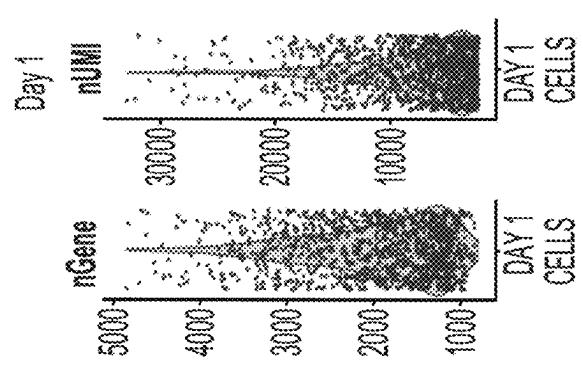
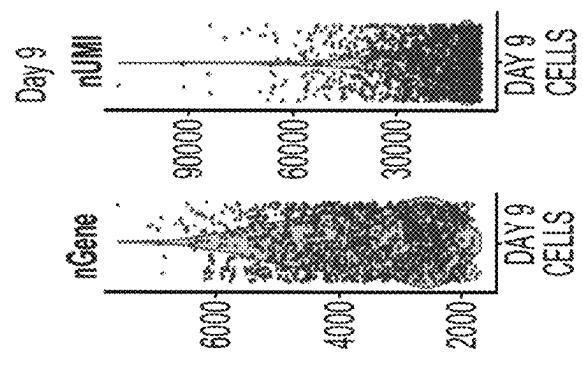
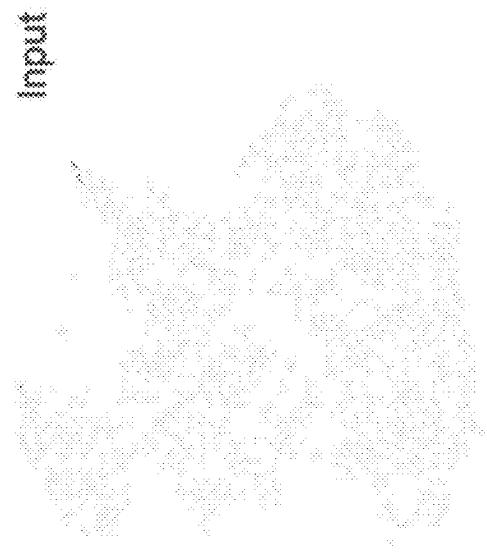


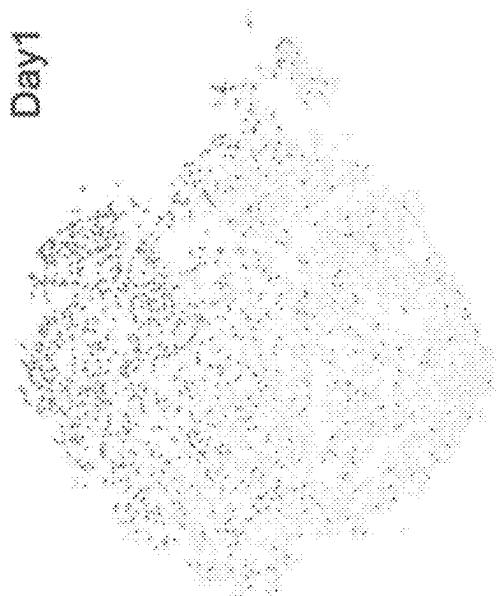
FIG. 23C



**FIG. 24A**

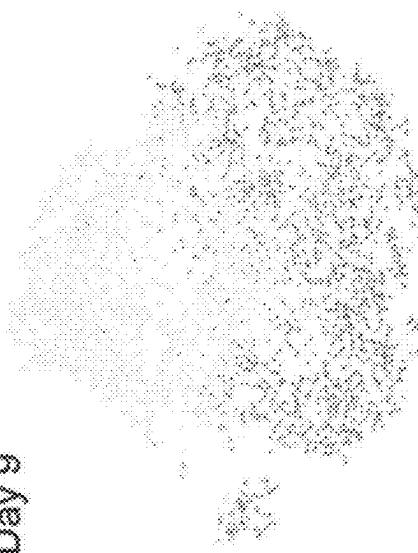


**FIG. 24B**



**Day 1**

**FIG. 24C**



**Day 9**

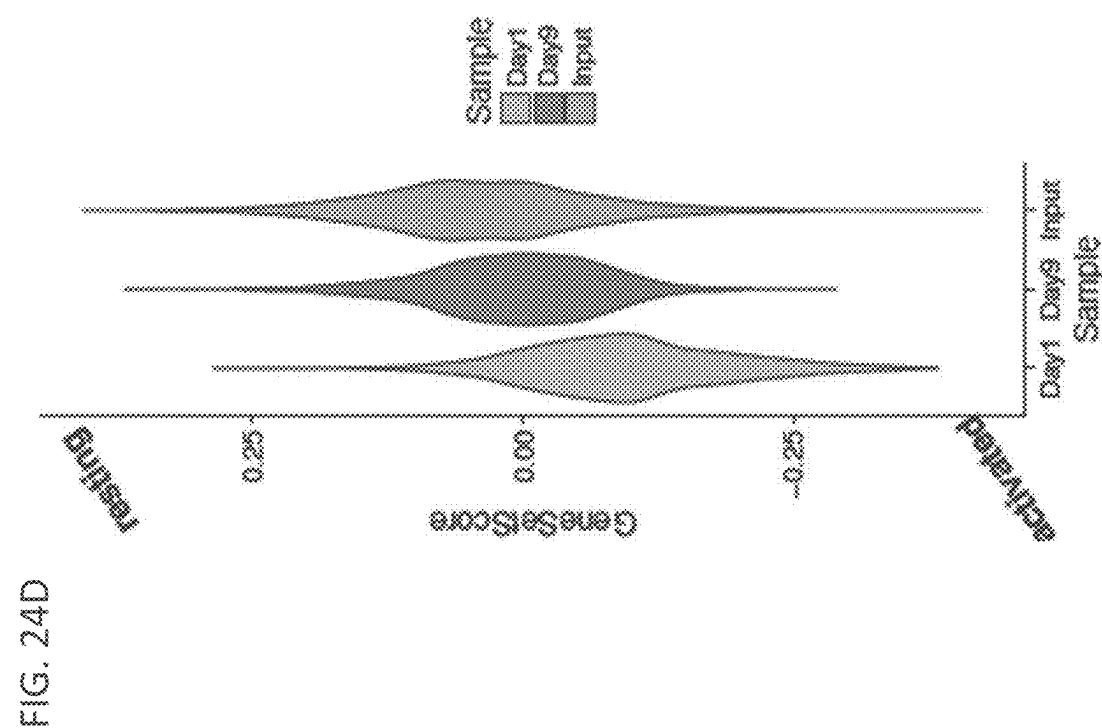


FIG. 24D

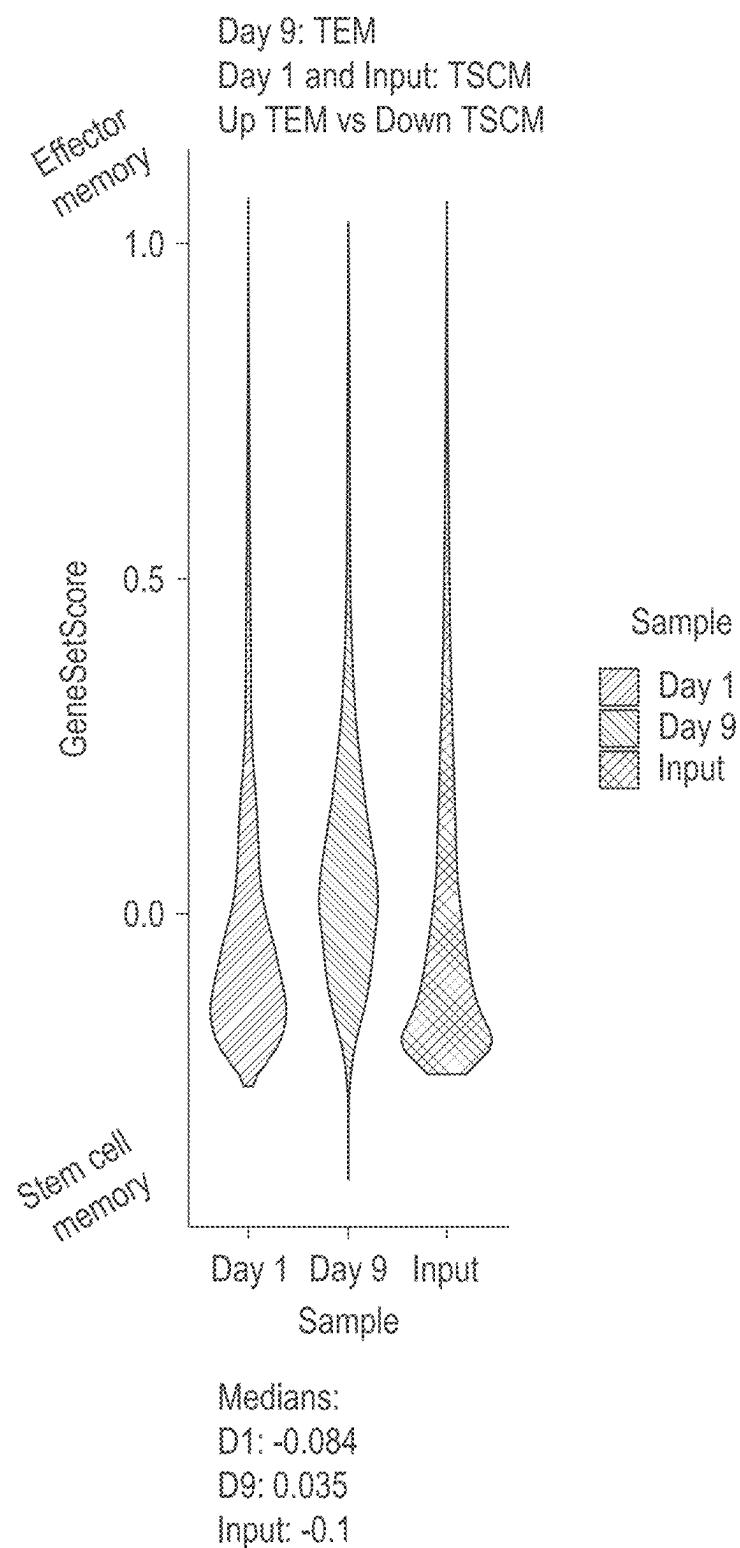
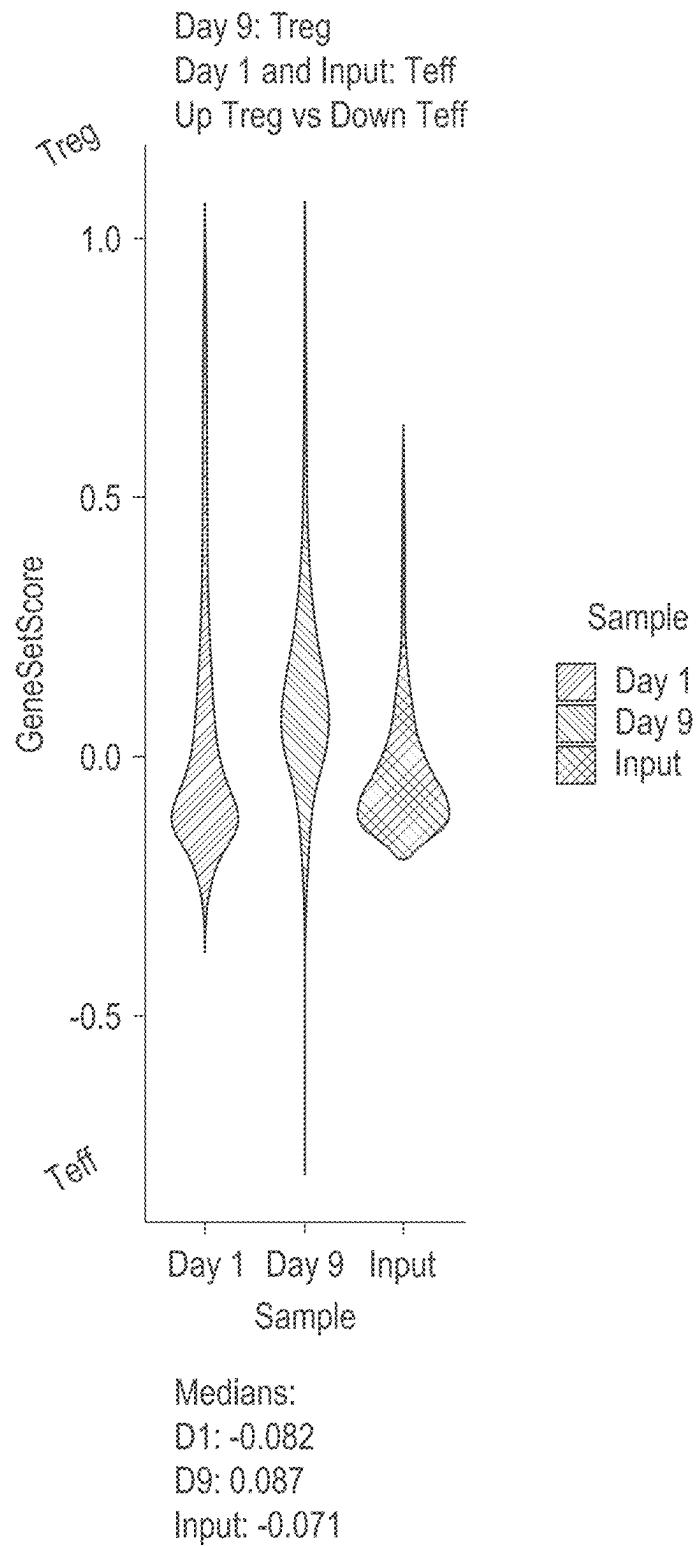


FIG. 25A



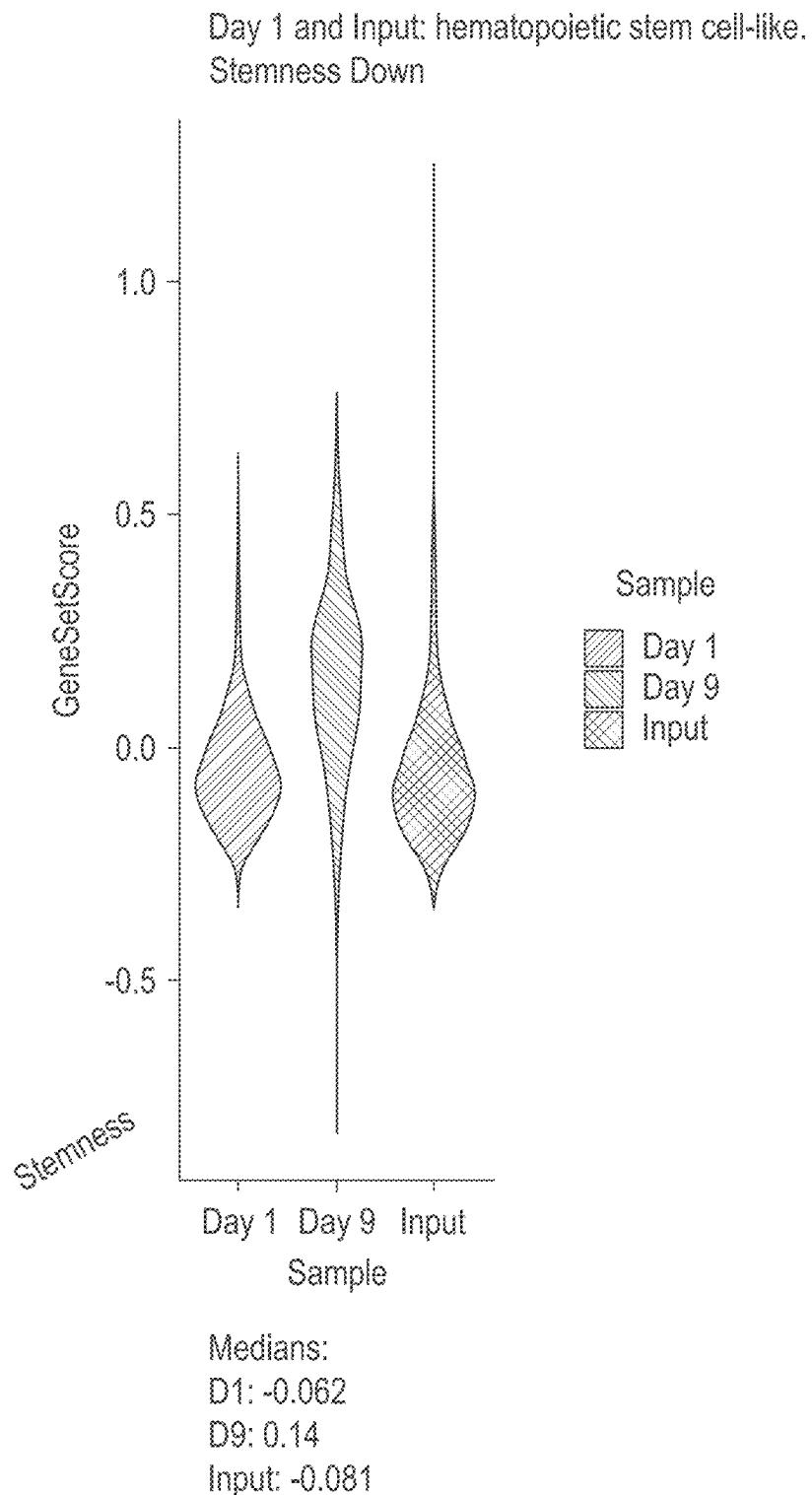


FIG. 25C

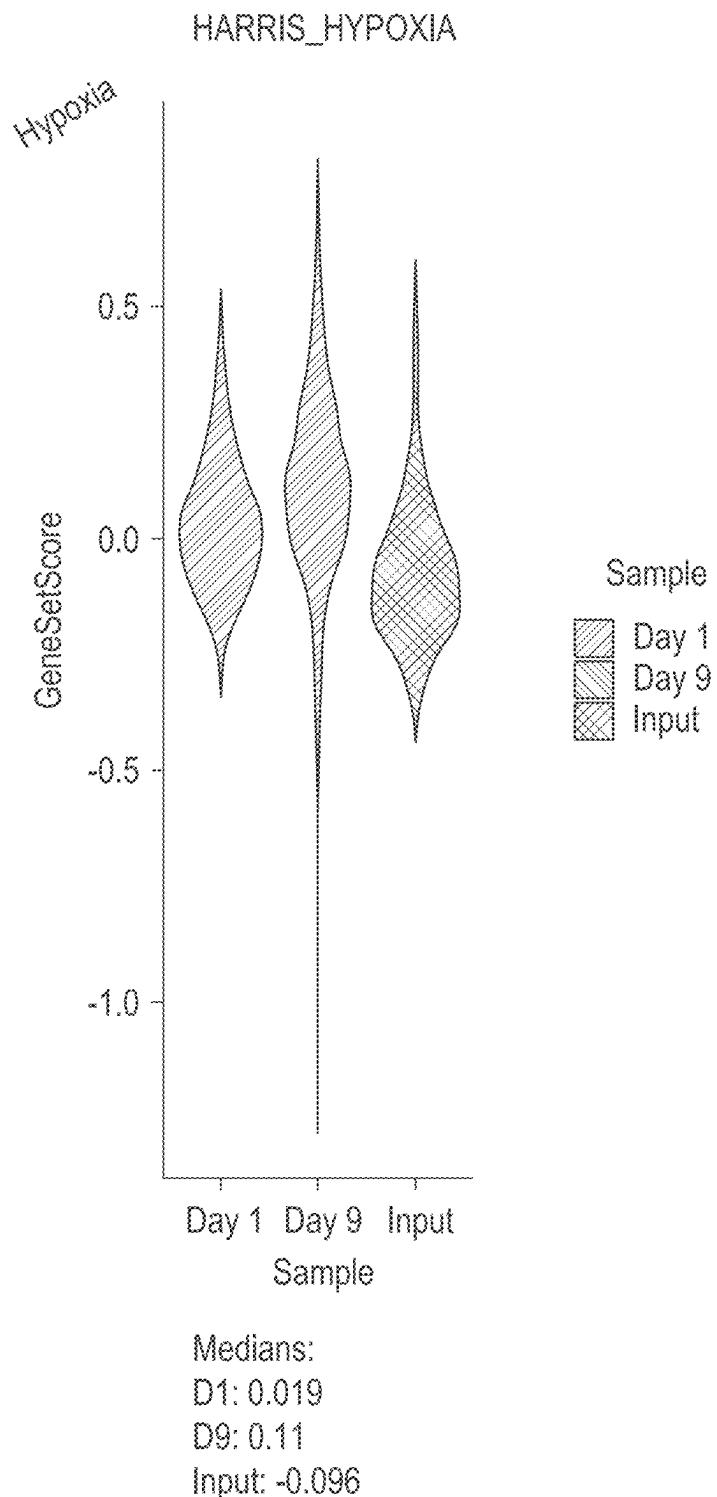


FIG. 25D

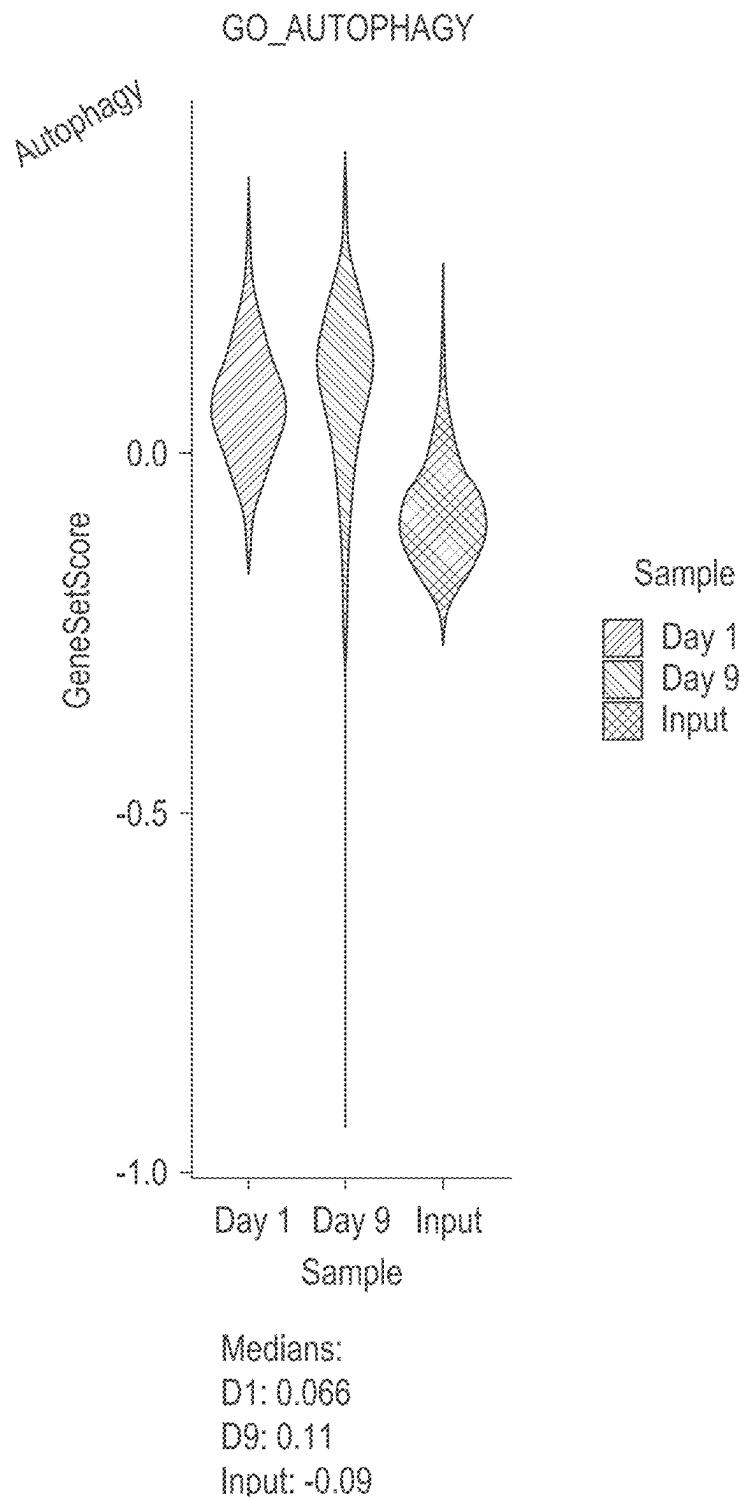


FIG. 25E

FIG. 26C

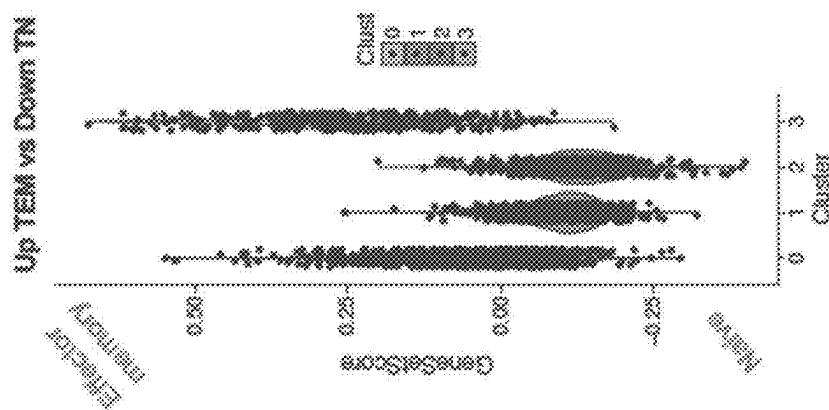


FIG. 26B

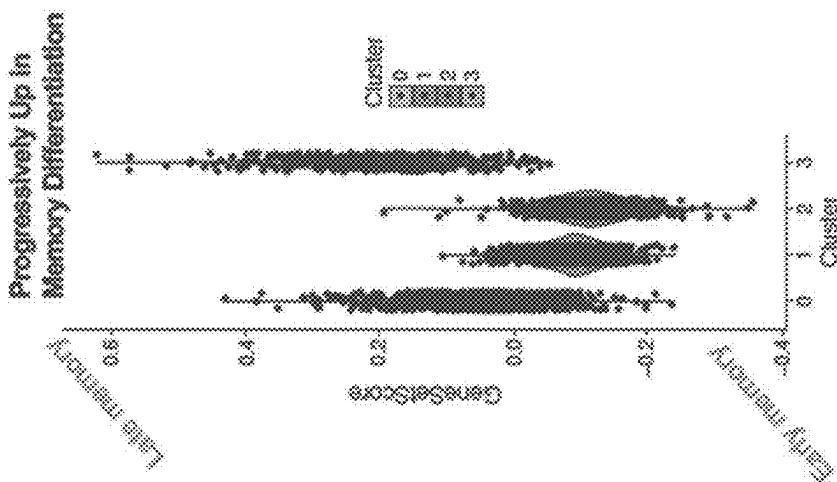


FIG. 26A

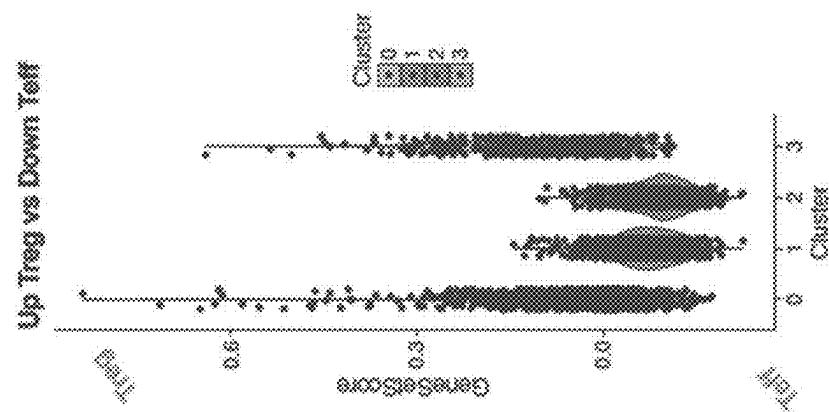


FIG. 27A

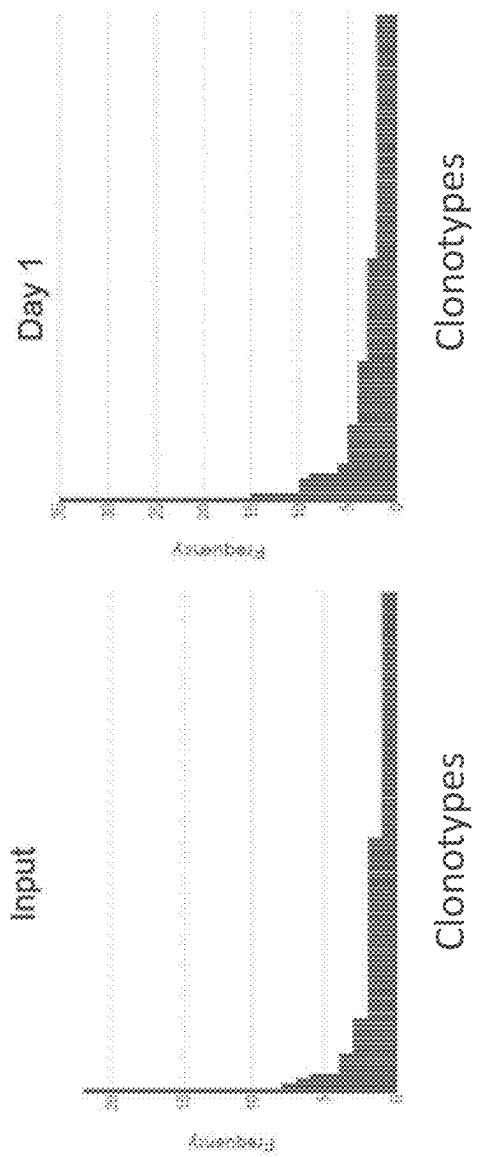


FIG. 27B

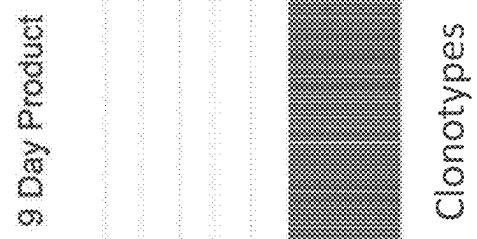
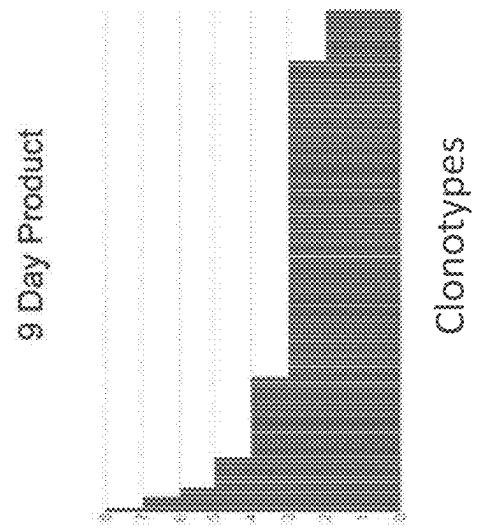


FIG. 28A

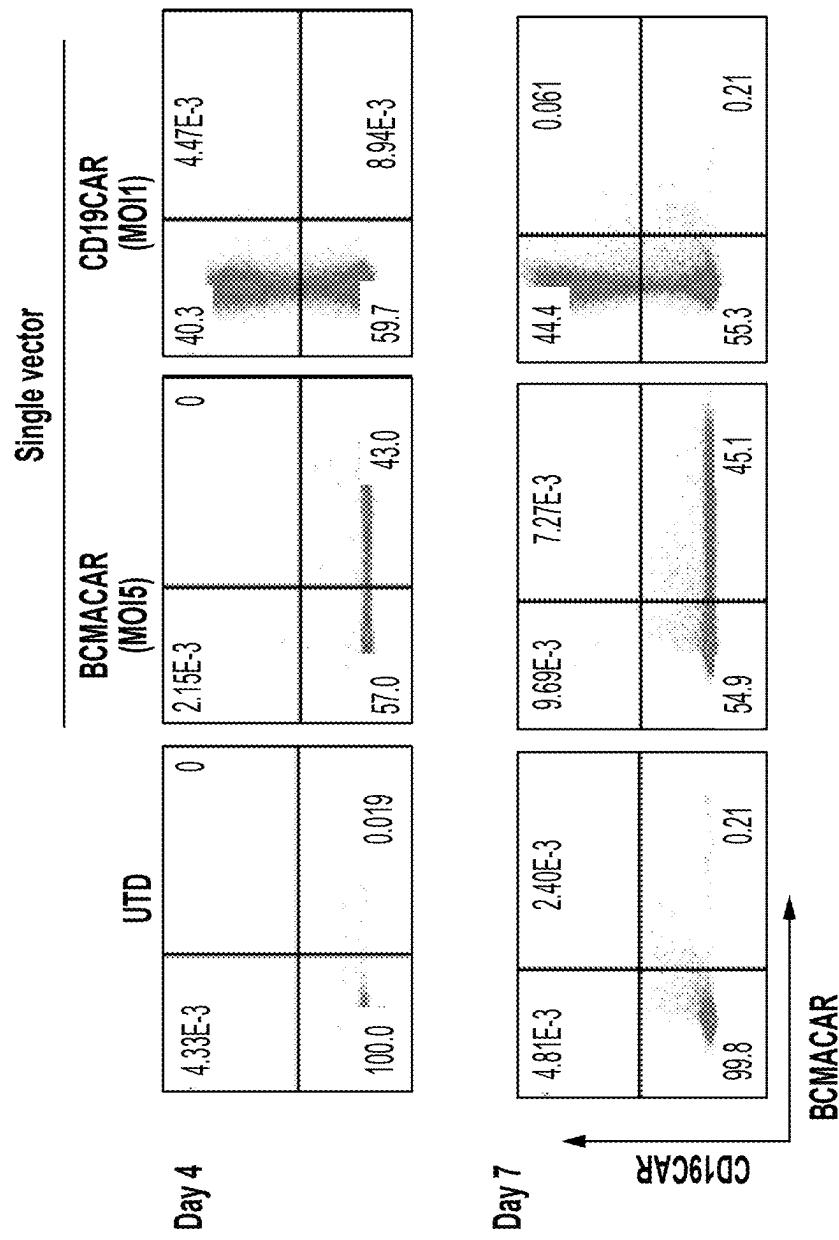


FIG. 28A CONT.

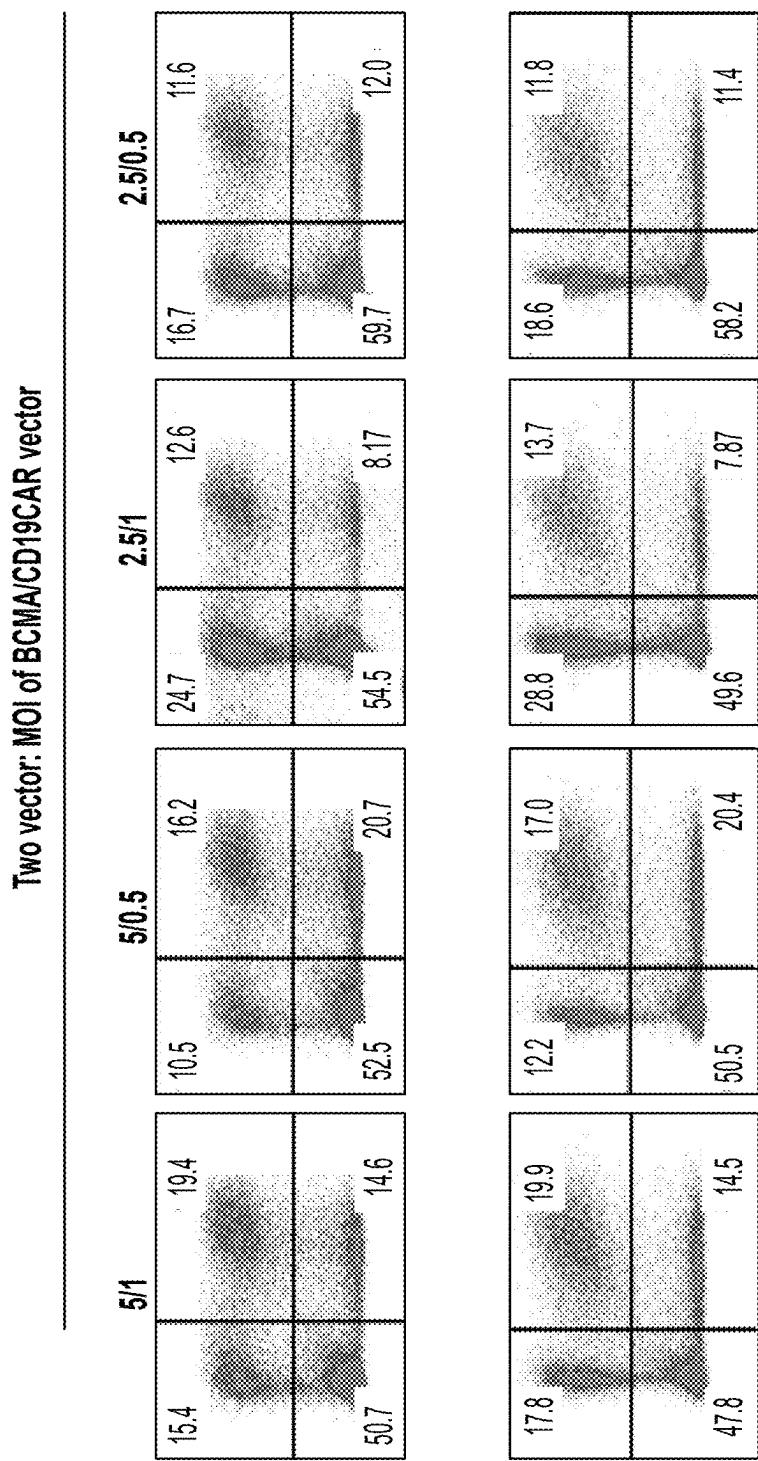
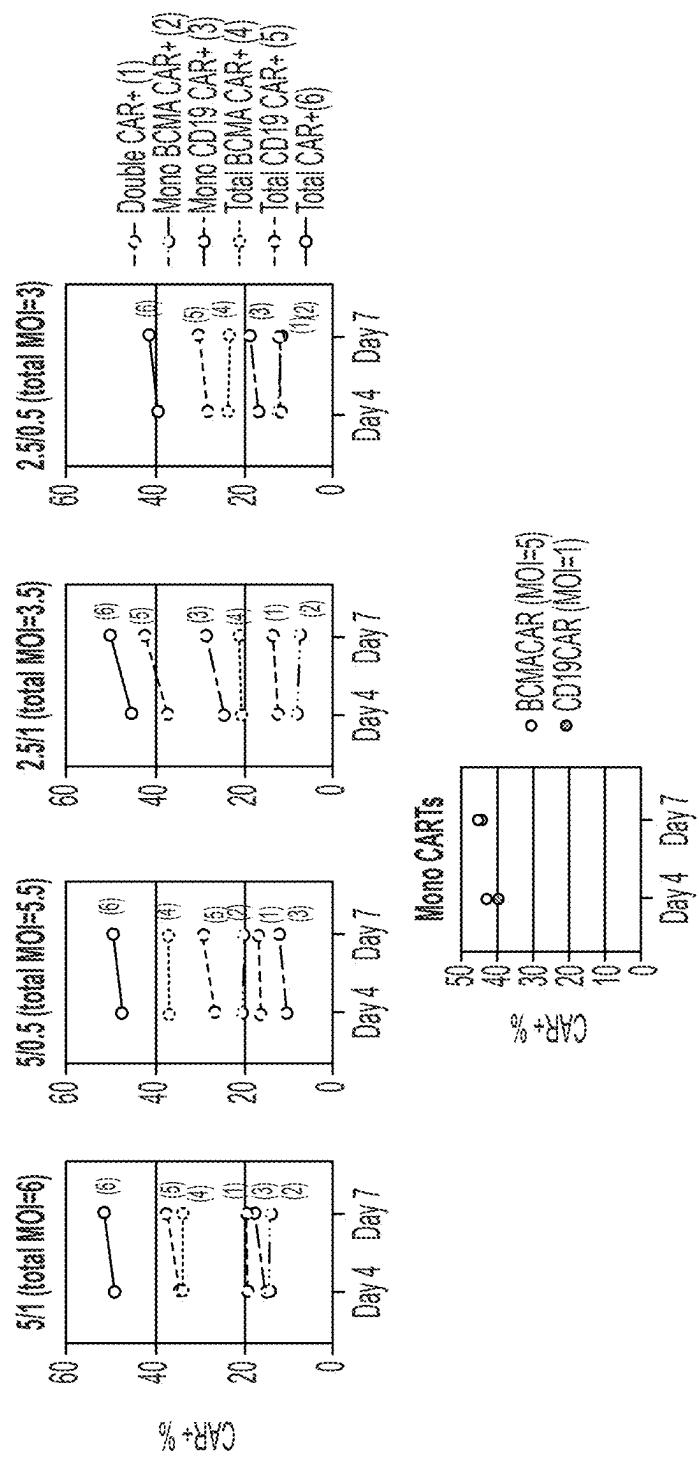


FIG. 28B



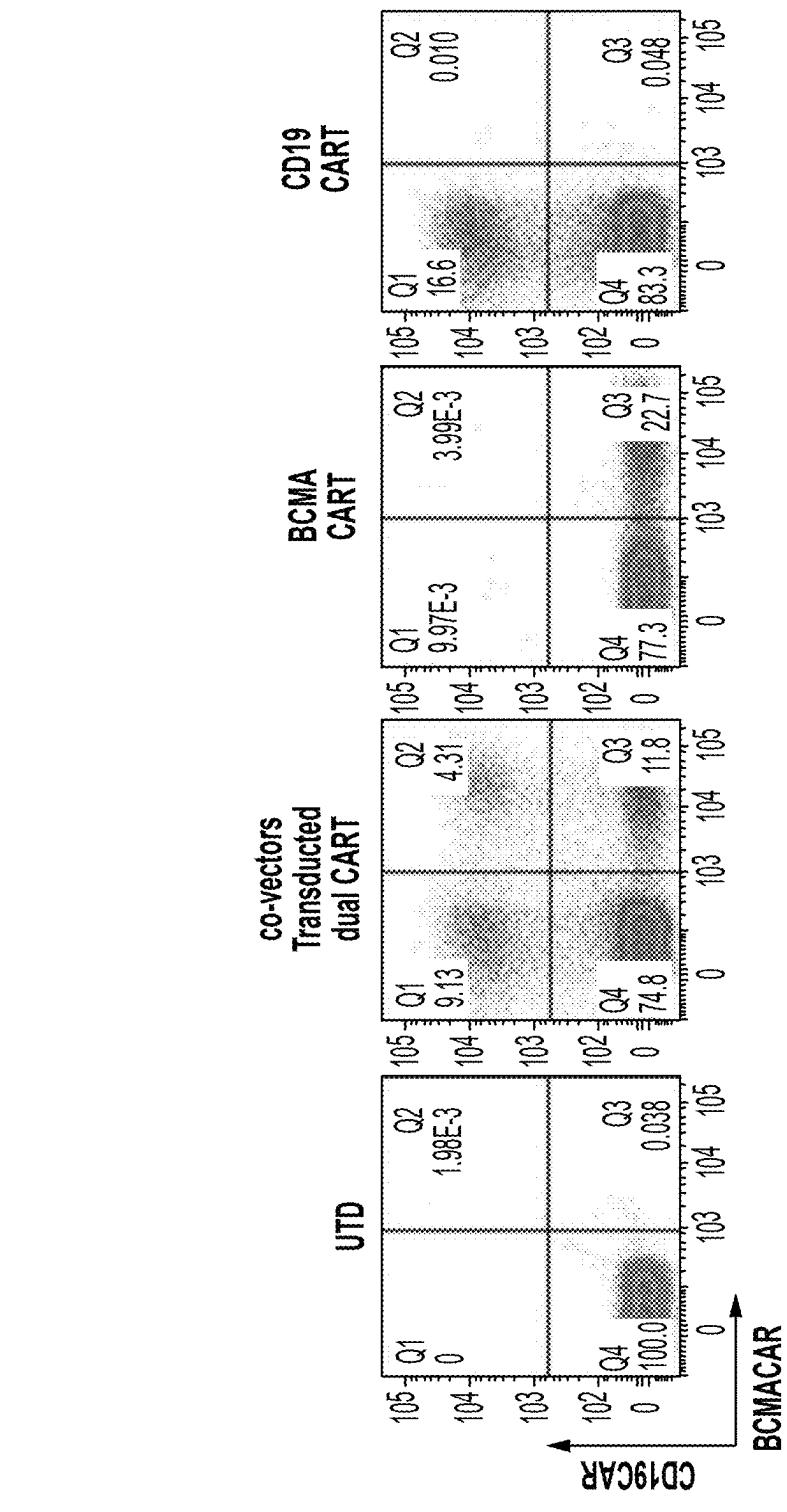
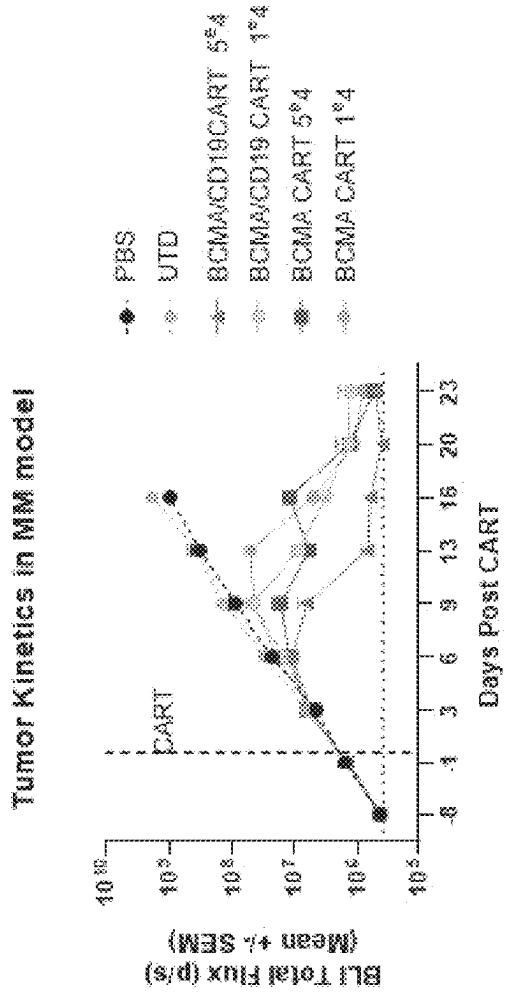
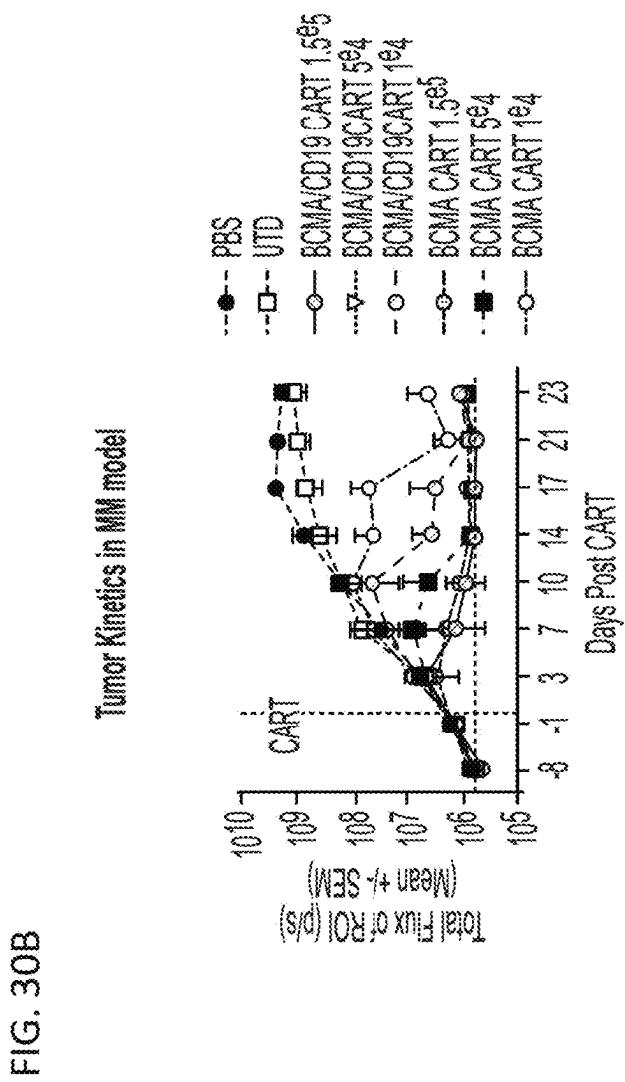
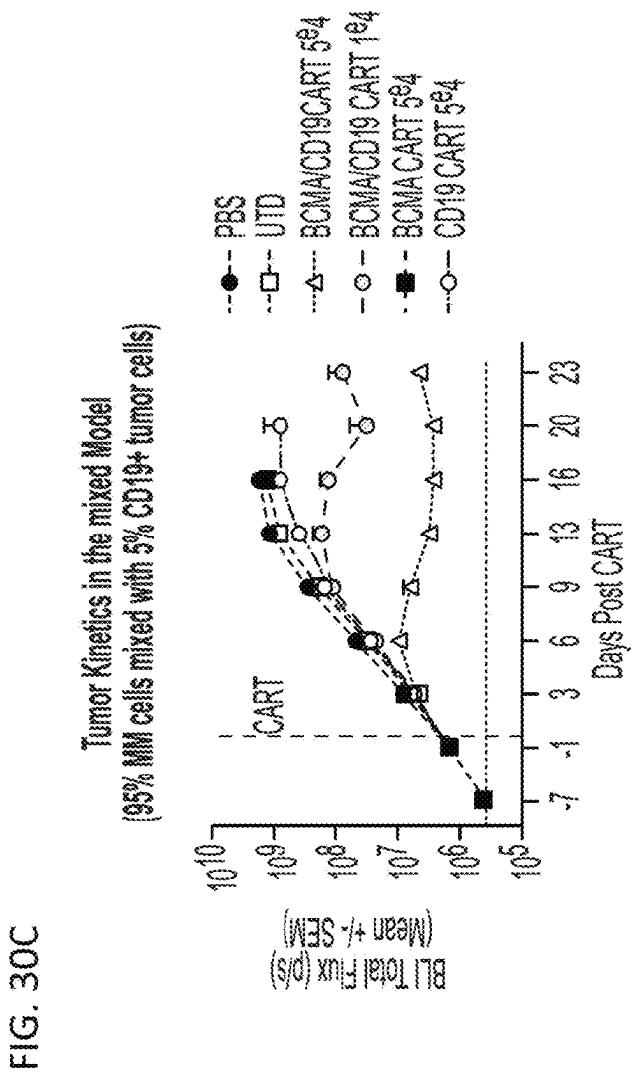


FIG. 29

FIG 30A







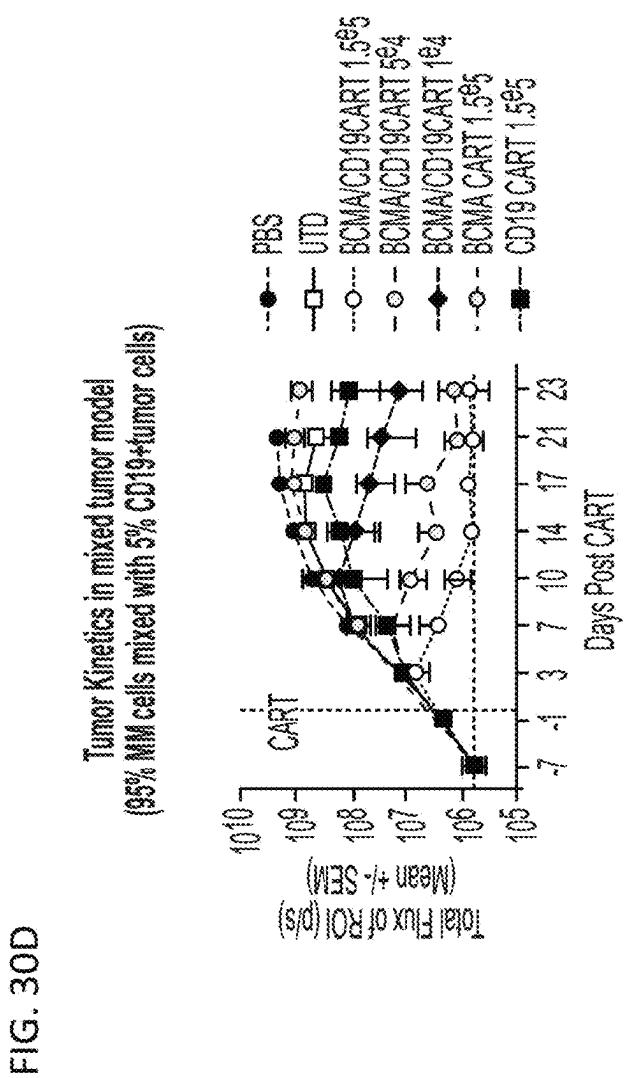
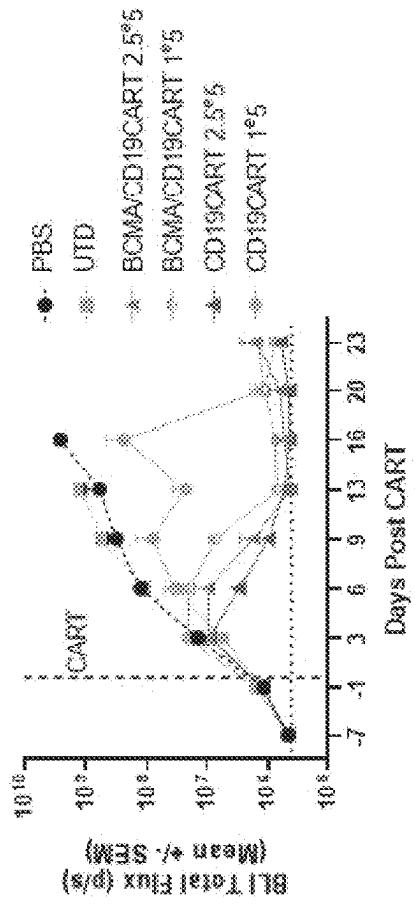


FIG. 30E

Tumor Kinetics in CD19<sup>+</sup>tumor model

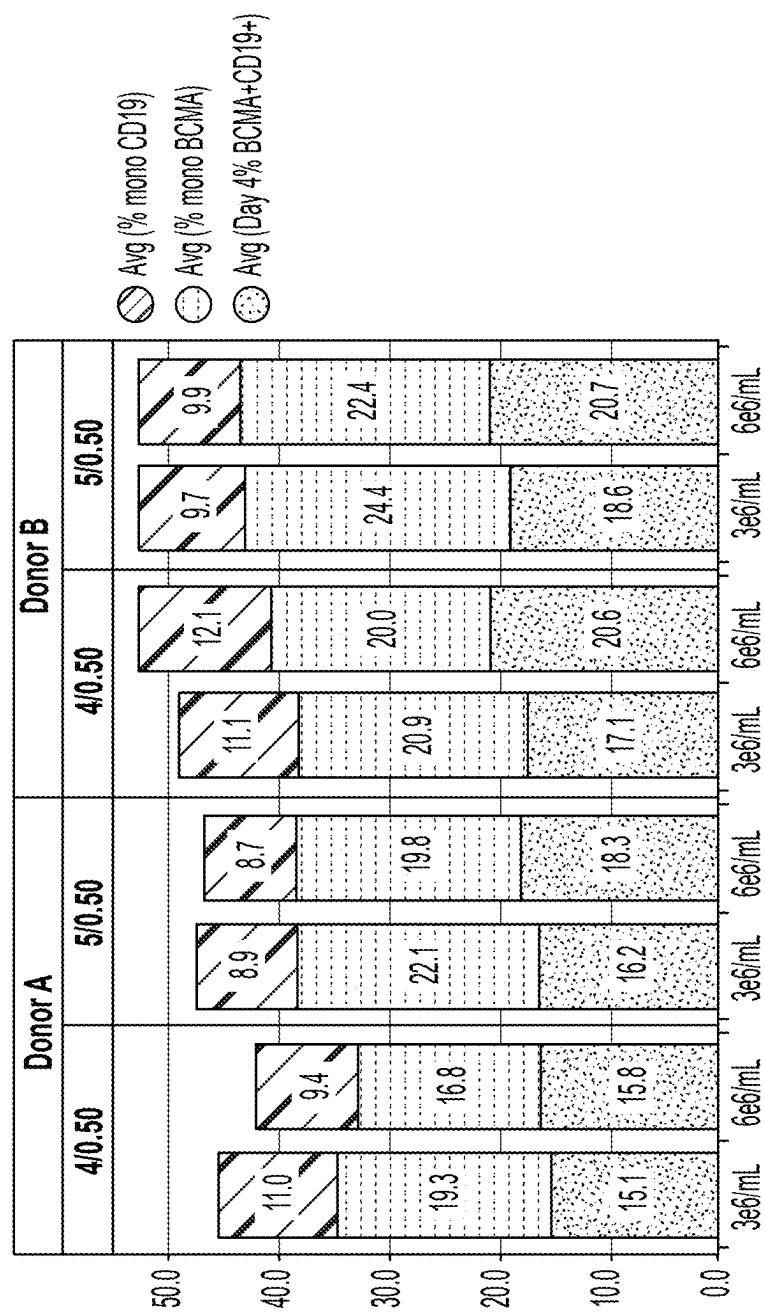


FIG. 31

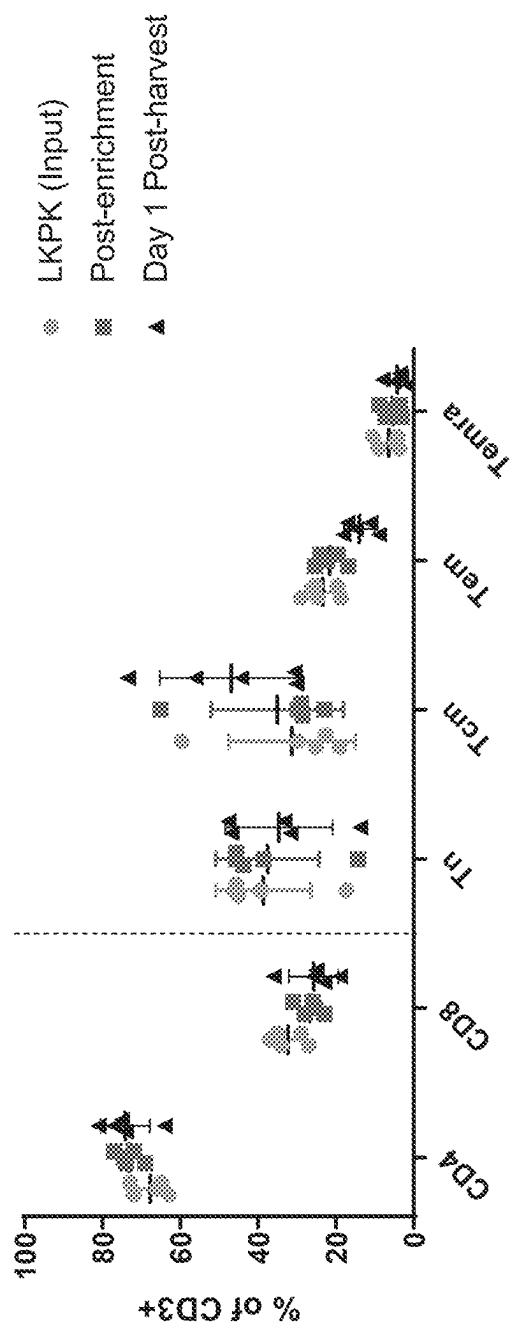
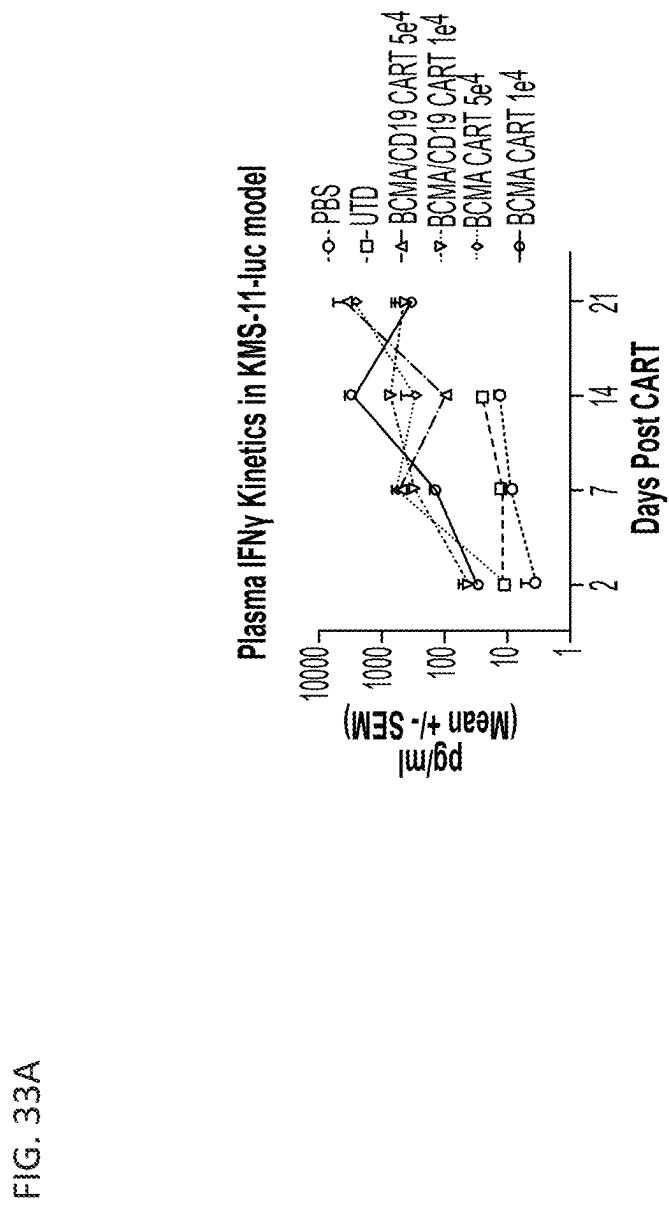


FIG. 32



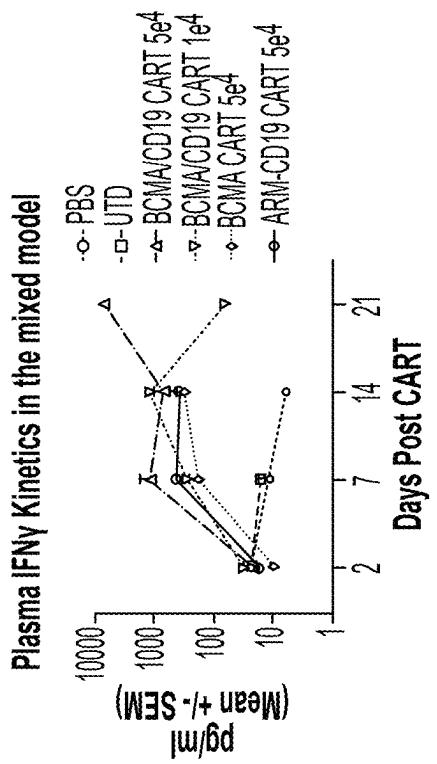


FIG. 33B

# CHIMERIC ANTIGEN RECEPTORS AND USES THEREOF

## CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Ser. No. 62/940, 509, filed on Nov. 26, 2019, the entire contents of which are incorporated herein by reference.

## SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on Nov. 24, 2020, is named N2067-716610\_SL.txt and is 585,242 bytes in size.

## FIELD OF THE INVENTION

The present invention relates generally to immune effector cells (for example, T cells or NK cells) engineered to express a Chimeric Antigen Receptor (CAR), and compositions and uses thereof.

## BACKGROUND OF THE INVENTION

Adoptive cell transfer (ACT) therapy with T cells, especially with T cells transduced with Chimeric Antigen Receptors (CARs), has shown promise in several hematologic cancer trials. There exists a need for methods and processes to improve production of the CAR-expressing cell therapy product, enhance product quality, and maximize the therapeutic efficacy of the product.

## SUMMARY OF THE INVENTION

In one aspect, this invention features a cell, e.g., an immune cell, e.g., a T cell or NK cell, comprising a first antigen-binding domain and a second antigen-binding domain. In some embodiments, the first antigen-binding domain is an anti-BCMA binding domain. In some embodiments, the anti-BCMA binding domain comprises an anti-BCMA binding sequence disclosed herein, e.g., a CDR, VH, VL, or scFv sequence disclosed in Tables 3-15, 19, 20, 22, 26 and 31. In some embodiments, the second antigen-binding domain is an anti-CD19 binding domain. In some embodiments, the anti-CD19 binding domain comprises an anti-CD19 binding sequence disclosed herein, e.g., a CDR, VH, VL, or scFv sequence disclosed in Tables 2, 19, 22, and 31.

In some embodiments, the present invention provides a cell comprising (a) a first antigen-binding domain which is an anti-BCMA binding domain, wherein the anti-BCMA binding domain comprises a heavy chain variable region (VH) comprising a heavy chain complementary determining region 1 (HC CDR1), a heavy chain complementary determining region 2 (HC CDR2), and a heavy chain complementary determining region 3 (HC CDR3), and a light chain variable region (VL) comprising a light chain complementary determining region 1 (LC CDR1), a light chain complementary determining region 2 (LC CDR2), and a light chain complementary determining region 3 (LC CDR3), wherein the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequences of: (i) SEQ ID NOs: 86, 130, 88, 95, 131, and 132, respectively; (ii) SEQ ID NOs: 44, 45, 84, 54, 55, and 56, respectively; or

(iii) SEQ ID NOs: 179, 180, 181, 147, 182, and 183, respectively; and (b) a second antigen-binding domain. In some embodiments, the first antigen-binding domain and the second antigen-binding domain are disposed in two chimeric antigen receptor (CARs). In some embodiments, the first antigen-binding domain and the second antigen-binding domain are disposed in one CAR.

In some embodiments, the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequences of SEQ ID NOs: 86, 130, 88, 95, 131, and 132, respectively. In some embodiments, the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequences of SEQ ID NOs: 86, 87, 88, 95, 96, and 97, respectively. In some embodiments, the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequences of SEQ ID NOs: 86, 109, 88, 95, 114, and 115, respectively. In some embodiments, the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequences of SEQ ID NOs: 86, 109, 88, 95, 114, and 97, respectively. In some embodiments, the VH comprises the amino acid sequence of SEQ ID NO: 93 or 112, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the VH is encoded by the nucleic acid sequence of SEQ ID NO: 260, 94 or 113, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the VL comprises the amino acid sequence of SEQ ID NO: 102, 118, or 124, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the VL is encoded by the nucleic acid sequence of SEQ ID NO: 261, 103, 119, or 125, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the VH and VL comprise the amino acid sequences of SEQ ID NOs: 93 and 102, respectively. In some embodiments, the VH and VL comprise the amino acid sequences of SEQ ID NOs: 112 and 118, respectively. In some embodiments, the VH and VL comprise the amino acid sequences of SEQ ID NOs: 112 and 124, respectively. In some embodiments, the first antigen-binding domain comprises a single-chain fragment variable (scFv) comprising the amino acid sequence of SEQ ID NO: 105, 120, or 126, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the first antigen-binding domain is encoded by the nucleic acid sequence of SEQ ID NO: 253, 106, 121, or 127, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the first antigen-binding domain is disposed in a first CAR. In some embodiments, the first CAR comprises the amino acid sequence of SEQ ID NO: 107, 226, 122, or 128, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the first CAR is encoded by the nucleic acid sequence of SEQ ID NO: 259, 258, 108, 123, or 129, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.

In some embodiments, the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequences of SEQ ID NOs: 44, 45, 84, 54, 55, and 56, respectively. In some embodiments, the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequences of SEQ ID NOs: 44, 45, 76, 54, 55, and 56, respectively. In some embodiments, the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequences of SEQ

ID NOs: 44, 45, 46, 54, 55, and 56, respectively. In some embodiments, the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequences of SEQ ID NOs: 44, 45, 68, 54, 55, and 56, respectively. In some embodiments, the VH comprises the amino acid sequence of SEQ ID NO: 78, 52, or 70, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the VH is encoded by the nucleic acid sequence of SEQ ID NO: 79, 53, or 71, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the VL comprises the amino acid sequence of SEQ ID NO: 61, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the VL is encoded by the nucleic acid sequence of SEQ ID NO: 62, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the VH and VL comprise the amino acid sequences of SEQ ID NOs: 78 and 61, respectively. In some embodiments, the VH and VL comprise the amino acid sequences of SEQ ID NOs: 52 and 61, respectively. In some embodiments, the VH and VL comprise the amino acid sequences of SEQ ID NOs: 70 and 61, respectively. In some embodiments, the first antigen-binding domain comprises a single-chain fragment variable (scFv) comprising the amino acid sequence of SEQ ID NO: 80, 64, or 72, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the first antigen-binding domain is encoded by the nucleic acid sequence of SEQ ID NO: 81, 65, or 73, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the first antigen-binding domain is disposed in a first CAR. In some embodiments, the first CAR comprises the amino acid sequence of SEQ ID NO: 224, 82, 66, or 74, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the first CAR is encoded by the nucleic acid sequence of SEQ ID NO: 83, 67, or 75, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.

In some embodiments, the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequences of SEQ ID NOs: 179, 180, 181, 147, 182, and 183, respectively. In some embodiments, the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequences of SEQ ID NOs: 137, 138, 139, 147, 148, and 149, respectively. In some embodiments, the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequences of SEQ ID NOs: 160, 161, 162, 147, 170, and 171, respectively. In some embodiments, the VH comprises the amino acid sequence of SEQ ID NO: 145 or 168, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the VH is encoded by the nucleic acid sequence of SEQ ID NO: 146 or 169, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the VL comprises the amino acid sequence of SEQ ID NO: 154 or 173, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the VL is encoded by the nucleic acid sequence of SEQ ID NO: 155 or 174, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the VH and VL comprise the amino acid sequences of SEQ ID NOs: 145 and 154, respectively. In some embodiments, the

VH and VL comprise the amino acid sequences of SEQ ID NOs: 168 and 173, respectively. In some embodiments, the first antigen-binding domain comprises a single-chain fragment variable (scFv) comprising the amino acid sequence of SEQ ID NO: 156 or 175, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the first antigen-binding domain is encoded by the nucleic acid sequence of SEQ ID NO: 157 or 176, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the first antigen-binding domain is disposed in a first CAR. In some embodiments, the first CAR comprises the amino acid sequence of SEQ ID NO: 158 or 177, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the first CAR is encoded by the nucleic acid sequence of SEQ ID NO: 159 or 178, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.

In some embodiments, provided herein is a cell comprising: (a) a first antigen-binding domain which is an anti-BCMA binding domain, wherein the anti-BCMA binding domain comprises: (i) a VH comprising a HC CDR1, HC CDR2, and HC CDR3 of an anti-BCMA sequence listed in Table 20 or 26 and a VL comprising a LC CDR1, LC CDR2, and LC CDR3 of an anti-BCMA sequence listed in Table 20 or 26, wherein the VH and VL are connected by a linker comprising the amino acid sequence of SEQ ID NO: 243; (ii) a VH and VL comprising the amino acid sequences of SEQ ID NOs: 239 and 242, respectively, wherein the VH and VL are connected by a linker comprising the amino acid sequence of SEQ ID NO: 243; or (iii) an scFv comprising the amino acid sequence of SEQ ID NO: 200; and (b) a second antigen-binding domain. In some embodiments, the first antigen-binding domain and the second antigen-binding domain are disposed in two chimeric antigen receptor (CARs). In some embodiments, the first antigen-binding domain and the second antigen-binding domain are disposed in one CAR. In some embodiments, the second antigen-binding domain binds to an antigen chosen from: CD19, CD5, CD10, CD20, CD21, CD22, CD23, CD24, CD25, CD27, CD30, CD34, CD37, CD38, CD40, CD53, CD69, CD72, CD73, CD74, CD75, CD77, CD79a, CD79b, CD80, CD81, CD82, CD83, CD84, CD85, CD86, CD123, CD135, CD138, CD179, CD269, Flt3, ROR1, FcRn5, FcRn2, CS-1, CXCR4, 5, 7, IL-7/3R, IL7/4/3R, or IL4R, optionally wherein the B cell antigen is chosen from CD19, CD20, CD22, FcRn5, FcRn2, CS-1, CD138, CD123, CD33, CD34, CLL-1, folate receptor beta, or FLT3. In some embodiments, the second antigen-binding domain binds to CD19. In some embodiments, the second antigen-binding domain binds to an antigen chosen from: EGFRvIII, mesothelin, GD2, Tn antigen, sTn antigen, Tn-O-Glycopeptides, sTn-O-Glycopeptides, PSMA, CD97, TAG72, CD44v6, CEA, EPCAM, KIT, IL-13Ra2, leguman, GD3, CD171, IL-11Ra, PSCA, MAD-CT-1, MAD-CT-2, VEGFR2, LewisY, CD24, PDGFR-beta, SSEA-4, folate receptor alpha, ERBBs (e.g., ERBB2), Her2/neu, MUC1, EGFR, NCAM, Ephrin B2, CAIX, LMP2, sLe, HMWMAA, o-acetyl-GD2, folate receptor beta, TEM1/CD248, TEM7R, FAP, Legumain, HPV E6 or E7, ML-IAP, CLDN6, TSHR, GPRC5D, ALK, Polysialic acid, Fos-related antigen, neutrophil elastase, TRP-2, CYP1B1, sperm protein 17, beta human chorionic gonadotropin, AFP, thyroglobulin, PLAC1, globoH, RAGE1, MN-CA IX, human telomerase reverse transcriptase, intestinal carboxyl esterase, mut hsp 70-2, NA-17, NY-BR-1, UPK2, HAVCR1, ADRB3, PANX3, NY-ESO-1,

GPR20, Ly6k, OR51E2, TARP, GFR $\alpha$ 4, or a peptide of any of these antigens presented on MHC.

In some embodiments, the second antigen-binding domain binds to CD19. In some embodiments, the second antigen-binding domain comprises a HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and/or LC CDR3 of an anti-CD19 sequence listed in Table 19 or Table 22, for example, a HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprising the amino acid sequences of SEQ ID NOS: 295 and 245-249, respectively. In some embodiments, the second antigen-binding domain comprises a VH and/or VL of an anti-CD19 sequence listed in Table 19 or Table 22, for example, a VH and VL comprising the amino acid sequences of SEQ ID NOS: 250 and 251, respectively, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the second antigen-binding domain comprises a scFv of an anti-CD19 sequence listed in Table 19 or Table 22, for example, a scFv comprising the amino acid sequence of SEQ ID NO: 211, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the second antigen-binding domain is disposed in a second CAR, wherein the CAR comprises a CAR of an anti-CD19 sequence listed in Table 19 or Table 22, for example, a CAR comprising the amino acid sequence of SEQ ID NO: 225 or 229, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.

In some embodiments, the first antigen-binding domain comprises a HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR comprising the amino acid sequences of (a) SEQ ID NOS: 86, 87, 88, 95, 96, and 97, respectively; (b) SEQ ID NOS: 44, 45, 76, 54, 55, and 56, respectively; or (c) SEQ ID NOS: 44, 45, 46, 54, 55, and 56, respectively. In some embodiments, the second antigen-binding domain comprises a HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprising the amino acid sequences of SEQ ID NOS: 295 and 245-249, respectively. In some embodiments, the first antigen-binding domain comprises a VH and VL comprising the amino acid sequences of: (a) SEQ ID NOS: 93 and 102, respectively; (b) SEQ ID NOS: 78 and 61, respectively; or (c) SEQ ID NOS: 52 and 61, respectively. In some embodiments, the second antigen-binding domain comprises a VH and VL comprising the amino acid sequences of SEQ ID NOS: 250 and 251, respectively. In some embodiments, the first antigen-binding domain comprises a scFv comprising the amino acid sequence of SEQ ID NO: 105, 80, or 64. In some embodiments, the second antigen-binding domain comprises a scFv comprising the amino acid sequence of SEQ ID NO: 211. In some embodiments, the first antigen-binding domain is encoded by the nucleic acid sequence of SEQ ID NO: 253, 106, 81, or 65. In some embodiments, the second antigen-binding domain is encoded by the nucleic acid sequence of SEQ ID NO: 212.

In some embodiments, the first antigen-binding domain is disposed in a first CAR and the second antigen-binding domain is disposed in a second CAR. In some embodiments, the first CAR further comprises a first transmembrane domain and a first intracellular signaling domain. In some embodiments, the second CAR further comprises a second transmembrane domain and a second intracellular signaling domain.

In some embodiments, the first CAR is encoded by a first nucleic acid sequence and the second CAR is encoded by a

second nucleic acid sequence, wherein the first and second nucleic acid sequences are disposed on separate nucleic acid molecules.

In some embodiments, the first CAR is encoded by a first nucleic acid sequence and the second CAR is encoded by a second nucleic acid sequence, wherein the first and second nucleic acid sequences are disposed on a single nucleic acid molecule. In some embodiments, the single nucleic acid molecule comprises the following configuration in a 5' to 3' orientation: a nucleic acid sequence encoding the first antigen-binding domain-a nucleic acid sequence encoding a first transmembrane domain-a nucleic acid sequence encoding a first intracellular signaling domain-a nucleic acid sequence encoding a linker-a nucleic acid sequence encoding the second antigen-binding domain-a nucleic acid sequence encoding a second transmembrane domain-a nucleic acid sequence encoding a second intracellular signaling domain-a nucleic acid sequence encoding a linker-a nucleic acid sequence encoding the first antigen-binding domain-a nucleic acid sequence encoding a first transmembrane domain-a nucleic acid sequence encoding a first intracellular signaling domain.

In some embodiments, the linker comprises a self-cleavage site. In some embodiments, the linker comprises a P2A site, a T2A site, an E2A site, or an F2A site. In some embodiments, the linker comprises a P2A site. In some embodiments, the linker is encoded by the nucleic acid sequence of SEQ ID NO: 209, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the linker comprises the amino acid sequence of SEQ ID NO: 208, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the single nucleic acid molecule comprises the nucleic acid sequence of SEQ ID NO: 215, 217, 219, 221, or 223, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the single nucleic acid molecule encodes the amino acid sequence of SEQ ID NO: 214, 216, 218, 220, or 222, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.

In some embodiments, the first antigen-binding domain and the second antigen-binding domain are disposed in one CAR, wherein the CAR further comprises a transmembrane domain and an intracellular signaling domain. In some embodiments, the first antigen-binding domain comprises a first VH (VH1) and a first VL (VL1) and the second antigen-binding domain comprises a second VH (VH2) and a second VL (VL2). In some embodiments, the VH1, VL1, VH2, and VL2 are arranged in the following configuration from the N-terminus to the C-terminus: VH2-optionally linker 1 ("L1")-VL1 optionally linker 2 ("L2")-VH1-optionally linker 3 ("L3")-VL2. In some embodiments, the VH1, VL1, VH2, and VL2 are arranged in the following configuration from the N-terminus to the C-terminus: VH1-optionally L1-VH2-optionally L2-VL2-optionally L3-VL1. In some embodiments, the VH1, VL1, VH2, and VL2 are arranged in the following configuration from the N-terminus to the C-terminus: VL2-optionally L1-VL1-optionally L2-VH1-optionally L3-VH2. In some embodiments, the VH1, VL1, VH2, and VL2 are arranged in the following configuration from the N-terminus to the C-terminus: VL2-

optionally L1-VH1-optionally L2-VL1-optionally L3-VH2. In some embodiments, the VH1, VL1, VH2, and VL2 are arranged in the following configuration from the N-terminus to the C-terminus: VH2-optionally L1-VH1-optionally L2-VL1-optionally L3-VL2. In some embodiments, the VH1, VL1, VH2, and VL2 are arranged in the following configuration from the N-terminus to the C-terminus: VL1-optionally L1-VH2-optionally L2-VL2-optionally L3-VH1. In some embodiments, the VH1, VL1, VH2, and VL2 are arranged in the following configuration from the N-terminus to the C-terminus: VL1-optionally L1-VL2-optionally L2-VH2-optionally L3-VH1. In some embodiments, the VH1, VL1, VH2, and VL2 are arranged in the following configuration from the N-terminus to the C-terminus: VH1-optionally L1-VL2-optionally L2-VH2-optionally L3-VL1. In some embodiments, the VH1 and VL1 comprise the amino acid sequences of SEQ ID NOS: 93 and 102, respectively (or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto). In some embodiments, the VH1 and VL1 comprise the amino acid sequences of SEQ ID NOS: 333 and 334, respectively (or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto). In some embodiments, the VH1 and VL1 comprise the amino acid sequences of SEQ ID NOS: 78 and 61, respectively (or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto). In some embodiments, the VH1 and VL1 comprise the amino acid sequences of SEQ ID NOS: 335 and 336, respectively (or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto). In some embodiments, the VH2 and VL2 comprise the amino acid sequences of SEQ ID NOS: 250 and 251, respectively (or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto). In some embodiments, the VH2 and VL2 comprise the amino acid sequences of SEQ ID NOS: 331 and 332, respectively (or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto). In some embodiments, L1 or L3 comprises the amino acid sequence of SEQ ID NO: 5 (or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto). In some embodiments, L2 comprises the amino acid sequence of SEQ ID NO: 63 (or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto). In some embodiments, the CAR comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 321-330, or an amino acid sequence having at least 80, 85, 90, 95, or 99% identity thereto. In some embodiments, the CAR comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 339-348, or an amino acid sequence having at least 80, 85, 90, 95, or 99% identity thereto.

In some embodiments, the CAR is encoded by a nucleic acid molecule comprising the following configuration in a 5' to 3' orientation: a nucleic acid sequence encoding the first antigen-binding domain-optionally a nucleic acid sequence encoding a linker-a nucleic acid sequence encoding the second antigen-binding domain-a nucleic acid sequence encoding a transmembrane domain-a nucleic acid sequence encoding an intracellular signaling domain. In some embodiments, the CAR is encoded by a nucleic acid molecule comprising the following configuration in a 5' to 3' orientation: a nucleic acid sequence encoding the second antigen-binding domain-optionally a nucleic acid sequence encoding a linker-a nucleic acid sequence encoding the first antigen-binding domain-a nucleic acid sequence encoding a

transmembrane domain-a nucleic acid sequence encoding an intracellular signaling domain.

In some embodiments, the CAR comprises the following configuration in an N- to C-orientation: the first antigen-binding domain-optionally a linker-the second antigen-binding domain-a transmembrane domain-an intracellular signaling domain. In some embodiments, the CAR comprises the following configuration in an N- to C-orientation: the second antigen-binding domain-optionally a linker-the first antigen-binding domain-a transmembrane domain-an intracellular signaling domain.

In some embodiments, the first antigen-binding domain or second antigen-binding domain comprises a VH and a VL. In some embodiments, the VH and VL are connected by a linker. In some embodiments, the linker comprises the amino acid sequence of SEQ ID NO: 5, 63, 104, or 243, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.

In some embodiments, the transmembrane domain, first transmembrane domain, or second transmembrane domain comprises a transmembrane domain of a protein chosen from the alpha, beta or zeta chain of T-cell receptor, CD28, CD3 epsilon, CD45, CD4, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137 or CD154. In some embodiments, the transmembrane domain, first transmembrane domain, or second transmembrane domain comprises the amino acid sequence of SEQ ID NO: 6, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the transmembrane domain, first transmembrane domain, or second transmembrane domain is encoded by the nucleic acid sequence of SEQ ID NO: 17, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.

In some embodiments, the first antigen-binding domain or second antigen-binding domain is connected to the transmembrane domain, first transmembrane domain, or second transmembrane domain by a hinge region (e.g., a first or second hinge region). In some embodiments, the hinge region comprises the amino acid sequence of SEQ ID NO: 2, 3, or 4, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the hinge region is encoded by the nucleic acid sequence of SEQ ID NO: 13, 14, or 15, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the hinge region and the transmembrane domain comprise the amino acid sequence of SEQ ID NO: 202, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the hinge region and the transmembrane domain are encoded by the nucleic acid sequence of SEQ ID NO: 203 or 213, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.

In some embodiments, the intracellular signaling domain, first intracellular signaling domain, or second intracellular signaling domain comprises a primary signaling domain (e.g., a first or second primary signaling domain). In some embodiments, the primary signaling domain comprises a functional signaling domain derived from CD3 zeta, TCR zeta, FcR gamma, FcR beta, CD3 gamma, CD3 delta, CD3 epsilon, CD5, CD22, CD79a, CD79b, CD278 (ICOS), FcERI, DAP10, DAP12, or CD66d. In some embodiments, the primary signaling domain comprises the amino acid sequence of SEQ ID NO: 9 or 10, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the primary signal-

ing domain is encoded by the nucleic acid sequence of SEQ ID NO: 20, 21, or 205, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the intracellular signaling domain, first intracellular signaling domain, or second intracellular signaling domain comprises a costimulatory signaling domain (e.g., a first or second costimulatory signaling domain). In some embodiments, the costimulatory signaling domain comprises a functional signaling domain derived from a MHC class I molecule, a TNF receptor protein, an Immunoglobulin-like protein, a cytokine receptor, an integrin, a signalling lymphocytic activation molecule (SLAM protein), an activating NK cell receptor, BTLA, a Toll ligand receptor, OX40, CD2, CD7, CD27, CD28, CD30, CD40, CDS, ICAM-1, 4-1BB (CD137), B7-H3, ICOS (CD278), GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD4, CD8alpha, CD8beta, IL2R beta, IL2R gamma, IL7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, ITGB7, NKG2D, NKG2C, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, CD28-OX40, CD28-4-1BB, or a ligand that specifically binds with CD83. In some embodiments, the costimulatory signaling domain comprises the amino acid sequence of SEQ ID NO: 7, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the costimulatory signaling domain is encoded by the nucleic acid sequence of SEQ ID NO: 18 or 204, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the intracellular signaling domain, first intracellular signaling domain, or second intracellular signaling domain comprises a functional signaling domain derived from 4-1BB and a functional signaling domain derived from CD3 zeta. In some embodiments, the intracellular signaling domain, first intracellular signaling domain, or second intracellular signaling domain comprises the amino acid sequence of SEQ ID NO: 7 (or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto) and the amino acid sequence of SEQ ID NO: 9 or 10 (or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto). In some embodiments, the intracellular signaling domain, first intracellular signaling domain, or second intracellular signaling domain comprises the amino acid sequence of SEQ ID NO: 7 and the amino acid sequence of SEQ ID NO: 9 or 10.

In some embodiments, the CAR, first CAR, or second CAR further comprises a leader sequence (e.g., a first or second leader sequence). In some embodiments, the leader sequence comprises the amino acid sequence of SEQ ID NO: 1, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the leader sequence is encoded by the nucleic acid sequence of SEQ ID NO: 199 or 210, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.

In some embodiments, the first leader sequence and the second leader sequence are encoded by different nucleic acid sequences (e.g., differ by at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, or 100%). In some

embodiments, the first hinge region and the second hinge region are encoded by different nucleic acid sequences (e.g., differ by at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, or 100%). In some embodiments, the first transmembrane domain and the second transmembrane domain are encoded by different nucleic acid sequences (e.g., differ by at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, or 100%). In some embodiments, the first intracellular signaling domain and the second intracellular signaling domain are encoded by different nucleic acid sequences (e.g., differ by at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, or 100%). In some embodiments, the first primary signaling domain and the second primary signaling domain are encoded by different nucleic acid sequences (e.g., differ by at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, or 100%). In some embodiments, the first costimulatory signaling domain and the second costimulatory signaling domain are encoded by different nucleic acid sequences (e.g., differ by at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, or 100%). In some embodiments, the first leader sequence and the second leader sequence comprise the same amino acid sequence (e.g., the first leader sequence and the second leader sequence comprise the amino acid sequence of SEQ ID NO: 1, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto). In some embodiments, the first leader sequence and the second leader sequence comprise different amino acid sequences. In some embodiments, the first hinge region and the second hinge region comprise the same amino acid sequence (e.g., the first hinge region and the second hinge region comprise the amino acid sequence of SEQ ID NO: 2, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto). In some embodiments, the first hinge region and the second hinge region comprise different amino acid sequences. In some embodiments, the first transmembrane domain and the second transmembrane domain comprise the same amino acid sequence (e.g., the first transmembrane domain and the second transmembrane domain comprise the amino acid sequence of SEQ ID NO: 6, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto). In some embodiments, the first transmembrane domain and the second transmembrane domain comprise different amino acid sequences. In some embodiments, the first intracellular signaling domain and the second intracellular signaling domain comprise the same amino acid sequence. In some embodiments, the first intracellular signaling domain and the second intracellular signaling domain comprise different amino acid sequences. In some embodiments, the first primary signaling domain and the second primary signaling domain comprise the same amino acid sequence (e.g., the first primary signaling domain and the second primary signaling domain comprise the amino acid sequence of SEQ ID NO: 10, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto). In some embodiments, the first primary signaling domain and the second primary signaling domain comprise different amino acid sequences. In some embodiments, the first costimulatory signaling domain and the second costimulatory signaling domain comprise the same amino acid sequence (e.g., the first costimulatory signaling domain and the second costimulatory signaling domain comprise the amino acid sequence of SEQ ID NO: 7, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto). In some embodiments, the first costimula-

tory signaling domain and the second costimulatory signaling domain comprise different amino acid sequences (e.g., the first and second costimulatory signaling domains comprise a 4-1BB costimulatory domain sequence and a CD28 costimulatory domain sequence, respectively; or comprise a CD28 costimulatory domain sequence and a 4-1BB costimulatory domain sequence, respectively). In some embodiments, the first leader sequence and the second leader sequence are encoded by nucleic acid sequences comprising SEQ ID NOs: 199 and 210, respectively (or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto). In some embodiments, the first leader sequence and the second leader sequence are encoded by nucleic acid sequences comprising SEQ ID NOs: 210 and 199, respectively (or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto). In some embodiments, the first hinge region and the second hinge region are encoded by nucleic acid sequences comprising SEQ ID NOs: 337 and 13, respectively (or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto). In some embodiments, the first hinge region and the second hinge region are encoded by nucleic acid sequences comprising SEQ ID NOs: 13 and 337, respectively (or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto). In some embodiments, the first transmembrane domain and the second transmembrane domain are encoded by nucleic acid sequences comprising SEQ ID NOs: 338 and 17, respectively (or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto). In some embodiments, the first transmembrane domain and the second transmembrane domain are encoded by nucleic acid sequences comprising SEQ ID NOs: 17 and 338, respectively (or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto). In some embodiments, the first costimulatory signaling domain and the second costimulatory signaling domain are encoded by nucleic acid sequences comprising SEQ ID NOs: 204 and 18, respectively (or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto). In some embodiments, the first costimulatory signaling domain and the second costimulatory signaling domain are encoded by nucleic acid sequences SEQ ID NOs: 18 and 204, respectively (or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto). In some embodiments, the first primary signaling domain and the second primary signaling domain are encoded by nucleic acid sequences comprising SEQ ID NOs: 205 and 21, respectively (or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto). In some embodiments, the first primary signaling domain and the second primary signaling domain are encoded by nucleic acid sequences comprising SEQ ID NOs: 21 and 205, respectively (or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto).

In some embodiments, the CAR, first CAR, or second CAR is encoded by a nucleic acid molecule comprising a woodchuck hepatitis post-transcriptional regulatory element (WPRE).

In some embodiments, provided herein is a nucleic acid molecule comprising: (a) a first nucleic acid sequence encoding a first antigen-binding domain which is an anti-BCMA binding domain comprises a heavy chain variable region (VH) comprising a heavy chain complementary determining region 1 (HC CDR1), a heavy chain complementary determining region 2 (HC CDR2), and a heavy chain comple-

mentary determining region 3 (HC CDR3), and a light chain variable region (VL) comprising a light chain complementary determining region 1 (LC CDR1), a light chain complementary determining region 2 (LC CDR2), and a light chain complementary determining region 3 (LC CDR3), wherein the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequences of: (i) SEQ ID NOs: 86, 130, 88, 95, 131, and 132, respectively; (ii) SEQ ID NOs: 44, 45, 84, 54, 55, and 56, respectively; or (iii) SEQ ID NOs: 179, 180, 181, 147, 182, and 183, respectively; and (b) a second nucleic acid sequence encoding a second antigen-binding domain.

In some embodiments, the isolated nucleic acid molecule comprises a first nucleic acid molecule and a second nucleic acid molecule, which are separate nucleic acid molecules, and wherein the first nucleic acid sequence is disposed on the first nucleic acid molecule and the second nucleic acid sequence is disposed on the second nucleic acid molecule.

In some embodiments, provided herein is a nucleic acid molecule comprising: (a) a first nucleic acid sequence encoding a first antigen-binding domain which is an anti-BCMA binding domain, wherein the anti-BCMA binding domain comprises: (i) a VH comprising a HC CDR1, HC CDR2, and HC CDR3 of an anti-BCMA sequence listed in Table 20 or 26 and a VL comprising a LC CDR1, LC CDR2, and LC CDR3 of an anti-BCMA sequence listed in Table 20 or 26, wherein the VH and VL are connected by a linker comprising the amino acid sequence of SEQ ID NO: 243; (ii) a VH and VL comprising the amino acid sequences of SEQ ID NOs: 239 and 242, respectively, wherein the VH and VL are connected by a linker comprising the amino acid sequence of SEQ ID NO: 243; or (iii) an scFv comprising the amino acid sequence of SEQ ID NO: 200; and (b) a second nucleic acid sequence encoding a second antigen-binding domain.

In some embodiments, provided herein is a nucleic acid molecule comprising a first nucleic acid sequence encoding a first CAR and a second nucleic acid sequence encoding a second CAR, wherein the first CAR comprises a first antigen-binding domain which is an anti-BCMA binding domain, a first transmembrane domain, and a first intracellular signaling domain, and wherein the second CAR comprises a second antigen-binding domain which is an anti-CD19 binding domain, a second transmembrane domain, and a second intracellular signaling domain, wherein (i) the first antigen-binding domain comprises a HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR comprising the amino acid sequences of SEQ ID NOs: 86, 87, 88, 95, 96, and 97, respectively, and the second antigen-binding domain comprises a HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR comprising the amino acid sequences of SEQ ID NOs: 295 and 245-249, respectively; (ii) the first antigen-binding domain comprises a VH and VL comprising the amino acid sequences of SEQ ID NOs: 93 and 102, respectively, and the second antigen-binding domain comprises a VH and VL comprising the amino acid sequences of SEQ ID NOs: 250 and 251, respectively; (iii) the first antigen-binding domain comprises an scFv comprising the amino acid sequence of SEQ ID NO: 105, and the second antigen-binding domain comprises an scFv comprising the amino acid sequence of SEQ ID NO: 211; (iv) the first CAR comprises the amino acid sequence of SEQ ID NO: 107 or 226 and the second CAR comprises the amino acid sequence of SEQ ID NO: 225 or 229; or (v) the isolated nucleic acid molecule comprises the nucleic acid sequence of SEQ ID NO: 271.

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In some embodiments, provided herein is a nucleic acid molecule comprising a first nucleic acid sequence encoding a first CAR and a second nucleic acid sequence encoding a second CAR, wherein the first CAR comprises a first antigen-binding domain which is an anti-BCMA binding domain, a first transmembrane domain, and a first intracellular signaling domain, and wherein the second CAR comprises a second antigen-binding domain which is an anti-CD19 binding domain, a second transmembrane domain, and a second intracellular signaling domain, wherein: (i) the first antigen-binding domain comprises a HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR comprising the amino acid sequences of SEQ ID NOS: 44, 45, 76, 54, 55, and 56, respectively, the second antigen-binding domain comprises a HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprising the amino acid sequences of SEQ ID NOS: 295 and 245-249, respectively; (ii) the first antigen-binding domain comprises a VH and VL comprising the amino acid sequences of SEQ ID NOS: 78 and 61, respectively, and the second antigen-binding domain comprises a VH and VL comprising the amino acid sequences of SEQ ID NOS: 250 and 251, respectively; (iii) the first antigen-binding domain comprises an scFv comprising the amino acid sequence of SEQ ID NO: 80, and the second antigen-binding domain comprises an scFv comprising the amino acid sequence of SEQ ID NO: 211; (iv) the first CAR comprises the amino acid sequence of SEQ ID NO: 82 or 224 and the second CAR comprises the amino acid sequence of SEQ ID NO: 225 or 229; or (v) the isolated nucleic acid molecule comprises the nucleic acid sequence of SEQ ID NO: 215.

In some embodiments, provided herein is a polypeptide molecule encoded by a nucleic acid molecule disclosed herein.

In some embodiments, provided herein is a CAR, wherein the CAR comprises: (a) a first antigen-binding domain which is an anti-BCMA binding domain, wherein the anti-BCMA binding domain comprises a heavy chain variable region (VH) comprising a heavy chain complementary determining region 1 (HC CDR1), a heavy chain complementary determining region 2 (HC CDR2), and a heavy chain complementary determining region 3 (HC CDR3), and a light chain variable region (VL) comprising a light chain complementary determining region 1 (LC CDR1), a light chain complementary determining region 2 (LC CDR2), and a light chain complementary determining region 3 (LC CDR3), wherein the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequences of: (i) SEQ ID NOS: 86, 130, 88, 95, 131, and 132, respectively; (ii) SEQ ID NOS: 44, 45, 84, 54, 55, and 56, respectively; or (iii) SEQ ID NOS: 179, 180, 181, 147, 182, and 183, respectively; and (b) a second antigen-binding domain.

In some embodiments, provided herein is a CAR, wherein the CAR comprises: (a) a first antigen-binding domain which is an anti-BCMA binding domain, wherein the anti-BCMA binding domain comprises: (i) a VH comprising a HC CDR1, HC CDR2, and HC CDR3 of an anti-BCMA sequence listed in Table 20 or 26 and a VL comprising a LC CDR1, LC CDR2, and LC CDR3 of an anti-BCMA sequence listed in Table 20 or 26, wherein the VH and VL are connected by a linker comprising the amino acid sequence of SEQ ID NO: 243; (ii) a VH and VL comprising the amino acid sequences of SEQ ID NOS: 239 and 242, respectively, wherein the VH and VL are connected by a linker comprising the amino acid sequence of SEQ ID NO:

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243; or (iii) an scFv comprising the amino acid sequence of SEQ ID NO: 200; and (b) a second antigen-binding domain.

In some embodiments, provided herein is a vector comprising a nucleic acid molecule disclosed herein or a nucleic acid molecule encoding a CAR disclosed herein. In some embodiments, the vector is chosen from a DNA vector, a RNA vector, a plasmid, a lentivirus vector, an adenoviral vector, or a retrovirus vector. In some embodiments, the vector comprises an EF-1 promoter comprising the nucleic acid sequence of SEQ ID NO: 11.

In some embodiments, provided herein is a cell comprising a nucleic acid molecule disclosed herein, a nucleic acid molecule encoding a CAR disclosed herein, a polypeptide disclosed herein, a CAR disclosed herein, or a vector disclosed herein. In some embodiments, the cell is a T cell or an NK cell.

In some embodiments, disclosed herein is a method of making a cell comprising transducing a cell with a vector disclosed herein, optionally wherein the cell is a T cell or NK cell. In some embodiments, disclosed herein is a method of making an RNA-engineered cell comprising introducing an in vitro transcribed RNA or synthetic RNA into a cell, wherein the RNA comprises a nucleic acid molecule disclosed herein, a nucleic acid molecule encoding a CAR disclosed herein. In some embodiments, the cell is a T cell or NK cell.

In some embodiments, disclosed herein is a method of making a population of cells (for example, T cells) that express a chimeric antigen receptor (CAR), the method comprising: (i) contacting (for example, binding) a population of cells (for example, T cells, for example, T cells isolated from a frozen or fresh leukapheresis product) with an agent that stimulates a CD3/TCR complex and/or an agent that stimulates a costimulatory molecule on the surface of the cells; (ii) contacting the population of cells (for example, T cells) with a nucleic acid molecule disclosed herein, or a nucleic acid molecule encoding a CAR disclosed herein, thereby providing a population of cells (for example, T cells) comprising the nucleic acid molecule, and (iii) harvesting the population of cells (for example, T cells) for storage (for example, reformulating the population of cells in cryopreservation media) or administration, wherein:

(a) step (ii) is performed together with step (i) or no later than 20 hours after the beginning of step (i), for example, no later than 12, 13, 14, 15, 16, 17, or 18 hours after the beginning of step (i), for example, no later than 18 hours after the beginning of step (i), and step (iii) is performed no later than 30 (for example, 26)

hours after the beginning of step (i), for example, no later than 22, 23, 24, 25, 26, 27, 28, 29, or 30 hours after the beginning of step (i), for example, no later than 24 hours after the beginning of step (i),

(b) step (ii) is performed together with step (i) or no later than 20 hours after the beginning of step (i), for example, no later than 12, 13, 14, 15, 16, 17, or 18 hours after the beginning of step (i), for example, no later than 18 hours after the beginning of step (i), and step (iii) is performed no later than 30 hours after the beginning of step (ii), for example, no later than 22, 23, 24, 25, 26, 27, 28, 29, or 30 hours after the beginning of step (ii), or

(c) the population of cells from step (iii) are not expanded, or expanded by no more than 5, 10, 15, 20, 25, 30, 35, or 40%, for example, no more than 10%, for example, as assessed by the number of living cells, compared to the population of cells at the beginning of step (i),

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optionally wherein the nucleic acid molecule in step (ii) is on a viral vector, optionally wherein the nucleic acid molecule in step (ii) is an RNA molecule on a viral vector, optionally wherein step (ii) comprises transducing the population of cells (for example, T cells) with a viral vector comprising a nucleic acid molecule encoding the CAR.

In some embodiments, disclosed herein is a method of making a population of cells (for example, T cells) that express a chimeric antigen receptor (CAR), the method comprising: (1) contacting a population of cells (for example, T cells, for example, T cells isolated from a frozen leukapheresis product) with a cytokine chosen from IL-2, IL-7, IL-15 (for example, hetIL-15 (IL15/sIL-15Ra)), IL-21, IL-6 (for example, IL-6/SIL-6Ra), or a combination thereof, (2) contacting the population of cells (for example, T cells) with a nucleic acid molecule disclosed herein, or a nucleic acid molecule encoding a CAR disclosed herein, thereby providing a population of cells (for example, T cells) comprising the nucleic acid molecule, and (3) harvesting the population of cells (for example, T cells) for storage (for example, reformulating the population of cells in cryopreservation media) or administration, wherein:

- (a) step (2) is performed together with step (1) or no later than 5 hours after the beginning of step (1), for example, no later than 1, 2, 3, 4, or 5 hours after the beginning of step (1), and
- step (3) is performed no later than 26 hours after the beginning of step (1), for example, no later than 22, 23, or 24 hours after the beginning of step (1), for example, no later than 24 hours after the beginning of step (1), or
- (b) the population of cells from step (3) are not expanded, or expanded by no more than 5, 10, 15, 20, 25, 30, 35, or 40%, for example, no more than 10%, for example, as assessed by the number of living cells, compared to the population of cells at the beginning of step (1), optionally wherein the nucleic acid molecule in step (2) is on a viral vector, optionally wherein the nucleic acid molecule in step (ii) is an RNA molecule on a viral vector, optionally wherein step (ii) comprises transducing the population of cells (for example, T cells) with a viral vector comprising a nucleic acid molecule encoding the CAR.

In some embodiments, disclosed herein is a population of cells engineered to express a CAR ("a population of CAR-expressing cells"), said population comprising: (a) about the same percentage of naïve cells, for example, naïve T cells, for example, CD45RO- CCR7+ T cells, as compared to the percentage of naïve cells, for example, naïve T cells, for example, CD45RO- CCR7+ cells, in the same population of cells prior to being engineered to express the CAR; (b) a change within about 5% to about 10% of naïve cells, for example, naïve T cells, for example, CD45RO- CCR7+ T cells, for example, as compared to the percentage of naïve cells, for example, naïve T cells, for example, CD45RO- CCR7+ cells, in the same population of cells prior to being engineered to express the CAR; (c) an increased percentage of naïve cells, for example, naïve T cells, for example, CD45RO- CCR7+ T cells, for example, increased by at least 1.2, 1.4, 1.6, 1.8, 2.0, 2.2, 2.4, 2.6, 2.8, or 3-fold, as compared to the percentage of naïve cells, for example, naïve T cells, for example, CD45RO- CCR7+ cells, in the same population of cells prior to being engineered to express the CAR; (d) about the same percentage of central memory cells, for example, central memory T cells, for example, CCR7+CD45RO+ T cells, as compared to the percentage of

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central memory cells, for example, central memory T cells, for example, CCR7+CD45RO+ T cells, in the same population of cells prior to being engineered to express the CAR; (e) a change within about 5% to about 10% of central memory cells, for example, central memory T cells, for example, CCR7+CD45RO+ T cells, as compared to the percentage of central memory cells, for example, central memory T cells, for example, CCR7+CD45RO+ T cells, in the same population of cells prior to being engineered to express the CAR; (f) a decreased percentage of central memory cells, for example, central memory T cells, for example, CCR7+CD45RO+ T cells, for example, decreased by at least 20, 25, 30, 35, 40, 45, or 50%, as compared to the percentage of central memory cells, for example, central memory T cells, for example, CCR7+CD45RO+ T cells, in the same population of cells prior to being engineered to express the CAR; (g) about the same percentage of stem memory T cells, for example, CD45RA+CD95+IL-2 receptor  $\beta$ +CCR7+CD62L+ T cells, as compared to the percentage of stem memory T cells, for example, CD45RA+CD95+IL-2 receptor  $\beta$ +CCR7+CD62L+ T cells, in the same population of cells prior to being engineered to express the CAR; (h) a change within about 5% to about 10% of stem memory T cells, for example, CD45RA+CD95+IL-2 receptor  $\beta$ +CCR7+CD62L+ T cells, as compared to the percentage of stem memory T cells, for example, CD45RA+CD95+IL-2 receptor  $\beta$ +CCR7+CD62L+ T cells, in the same population of cells prior to being engineered to express the CAR; or (i) an increased percentage of stem memory T cells, for example, CD45RA+CD95+IL-2 receptor  $\beta$ +CCR7+CD62L+ T cells, as compared to the percentage of stem memory T cells, for example, CD45RA+CD95+IL-2 receptor  $\beta$ +CCR7+CD62L+ T cells, in the same population of cells prior to being engineered to express the CAR. In some embodiments, the population comprises a cell disclosed herein. In some embodiments, the population comprises a cell comprising a dual CAR or diabody CAR disclosed herein. In some embodiments, the population comprises a cell comprising (a) a first antigen-binding domain which is an anti-BCMA binding domain, wherein the anti-BCMA binding domain comprises a heavy chain variable region (VH) comprising a heavy chain complementary determining region 1 (HC CDR1), a heavy chain complementary determining region 2 (HC CDR2), and a heavy chain complementary determining region 3 (HC CDR3), and a light chain variable region (VL) comprising a light chain complementary determining region 1 (LC CDR1), a light chain complementary determining region 2 (LC CDR2), and a light chain complementary determining region 3 (LC CDR3), wherein the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequences of: (i) SEQ ID NOS: 86, 130, 88, 95, 131, and 132, respectively; (ii) SEQ ID NOS: 44, 45, 84, 54, 55, and 56, respectively; or (iii) SEQ ID NOS: 179, 180, 181, 147, 182, and 183, respectively; and (b) a second antigen-binding domain.

In some embodiments, disclosed herein is a pharmaceutical composition comprising a cell disclosed herein or a population of cells disclosed herein, and a pharmaceutically acceptable carrier.

In some embodiments, the population of cells is made by a method disclosed herein. In some embodiments, the population comprises:

- (a) a first population of cells comprising an anti-BCMA CAR but not an anti-CD19 CAR;
- (b) a second population of cells comprising an anti-CD19 CAR but not an anti-BCMA CAR; and

(c) a third population of cells comprising both an anti-BCMA CAR and an anti-CD19 CAR.

In some embodiments:

- (i) the total number of viable cells in the second and third populations combined is less than or equal to about 110% (e.g., less than or equal to about 105%, 100%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, 5%, 1%, or less) of the total number of viable cells in the first and third populations combined;
- (ii) the total number of viable cells in the first and third populations combined is greater than or equal to about 90% (e.g., greater than or equal to about 100%, 125%, 150%, 175%, 200%, 250%, 300%, 400%, 500%, 750%, 1000%, 2000%, 5000, 10000% or more) of the total number of viable cells in the second and third populations combined; and/or
- (iii) the total number of viable cells in the first and third populations combined is greater than or equal to about 5% (e.g., greater than or equal to about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90%) of the total number of viable cells in the population.

In some embodiments, the population further comprises a fourth population of cells that do not comprise a CAR.

In some embodiments:

- (i) the total number of viable cells in the second population is less than or equal to about 110% (e.g., less than or equal to about 105%, 100%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, 5%, 1%, or less) of the total number of viable cells in the first and third populations combined;
- (ii) the total number of viable cells in the second population is less than or equal to: about 45% to about 50% (e.g., about 47%); about 50 to about 55% (e.g., about 53%); about 60% to about 65% (e.g., about 63%); or about 80 to about 85% (e.g., about 82%) of the total number of viable cells in the first and third populations combined.

In some embodiments, disclosed herein is a method of providing an anti-tumor immunity in a subject comprising administering to the subject an effective amount of a cell disclosed herein, a population of cells disclosed herein, or a pharmaceutical composition disclosed herein. In some embodiments, disclosed herein is a method of treating a subject having a disease associated with expression of BCMA comprising administering to the subject an effective amount of a cell disclosed herein, a population of cells disclosed herein, or a pharmaceutical composition disclosed herein. In some embodiments, the disease associated with BCMA expression is: (i) a cancer or malignancy, or a precancerous condition chosen from one or more of a myelodysplasia, a myelodysplastic syndrome or a preleukemia, or (ii) a non-cancer related indication associated with expression of BCMA. In some embodiments, the disease is a hematologic cancer or a solid cancer. In some embodiments, the disease is chosen from: acute leukemia, B-cell acute lymphoid leukemia ("BALL"), T-cell acute lymphoid leukemia ("TALL"), acute lymphoid leukemia (ALL), chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL), B cell prolymphocytic leukemia, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, diffuse large B cell lymphoma, follicular lymphoma, hairy cell leukemia, small cell- or large cell-follicular lymphoma, malignant lymphoproliferative conditions, MALT lymphoma, mantle cell lymphoma, Marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin's lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Walden-

strom macroglobulinemia, prostate cancer (e.g., castrate-resistant or therapy-resistant prostate cancer, or metastatic prostate cancer), pancreatic cancer, lung cancer, a plasma cell proliferative disorder (e.g., asymptomatic myeloma (smoldering multiple myeloma or indolent myeloma), monoclonal gammopathy of undetermined significance (MGUS), Waldenstrom's macroglobulinemia, plasmacytoma (e.g., plasma cell dyscrasia, solitary myeloma, solitary plasmacytoma, extramedullary plasmacytoma, and multiple plasmacytoma), systemic amyloid light chain amyloidosis, or POEMS syndrome (also known as Crow-Fukase syndrome, Takatsuki disease, and PEP syndrome)), or a combination thereof. In some embodiments, the disease is multiple myeloma.

In some embodiments, the population of cells or pharmaceutical composition is administered to the subject at a dose of about  $1 \times 10^6$  to about  $1 \times 10^8$  (e.g., about  $2 \times 10^6$  to about  $5 \times 10^7$ , about  $5 \times 10^6$  to about  $2 \times 10^7$ , about  $1 \times 10^6$  to about  $1 \times 10^7$ , about  $1 \times 10^7$  to about  $1 \times 10^8$ , about  $1 \times 10^6$  to about  $3 \times 10^6$ , about  $2 \times 10^6$  to about  $4 \times 10^6$ , about  $3 \times 10^6$  to about  $5 \times 10^6$ , about  $4 \times 10^6$  to about  $6 \times 10^6$ , about  $5 \times 10^6$  to about  $7 \times 10^6$ , about  $6 \times 10^6$  to about  $8 \times 10^6$ , about  $7 \times 10^6$  to about  $9 \times 10^6$ , about  $8 \times 10^6$  to about  $1 \times 10^7$ , about  $9 \times 10^6$  to about  $2 \times 10^7$ , about  $1 \times 10^7$  to about  $3 \times 10^7$ , about  $2 \times 10^7$  to about  $4 \times 10^7$ , about  $3 \times 10^7$  to about  $5 \times 10^7$ , about  $4 \times 10^7$  to about  $6 \times 10^7$ , about  $5 \times 10^7$  to about  $7 \times 10^7$ , about  $6 \times 10^7$  to about  $8 \times 10^7$ , about  $7 \times 10^7$  to about  $9 \times 10^7$ , about  $8 \times 10^7$  to about  $1 \times 10^8$ , about  $1 \times 10^6$  to about  $2 \times 10^6$ , about  $3 \times 10^6$  to about  $4 \times 10^6$ , about  $5 \times 10^6$  to about  $6 \times 10^6$ , about  $7 \times 10^6$  to about  $8 \times 10^6$ , about  $9 \times 10^6$  to about  $1 \times 10^7$ , about  $2 \times 10^7$  to about  $3 \times 10^7$ , about  $4 \times 10^7$  to about  $5 \times 10^7$ , about  $6 \times 10^7$  to about  $7 \times 10^7$ , about  $8 \times 10^7$  to about  $9 \times 10^7$ , or about  $1 \times 10^8$ ) CAR-positive viable cells (e.g., BCMA CAR+ T cells). In some embodiments, the population of cells or pharmaceutical composition is administered to the subject at a dose of about  $5 \times 10^6$  to about  $2 \times 10^7$  CAR-positive viable cells (e.g., BCMA CAR+ T cells).

In some embodiments, the population of cells or pharmaceutical composition is administered to the subject in one or more (e.g., 2, 3, 4, or more) doses. In some embodiments, the population of cells or pharmaceutical composition is administered to the subject in two doses. In some embodiments, the one or more doses comprises a first dose and a second dose, wherein the number of CAR-positive viable cells (e.g., BCMA CAR+ T cells) in the first dose is greater than, equal to, or less than the number of CAR-positive viable cells (e.g., BCMA CAR+ T cells) in the second dose.

In some embodiments, the one or more doses comprise a first dose and a second dose, wherein:

- (a) the first dose comprises about  $1 \times 10^6$  to about  $1 \times 10^7$  (e.g., about  $2 \times 10^6$  to about  $8 \times 10^6$ , about  $4 \times 10^6$  to about  $6 \times 10^6$ , about  $1 \times 10^6$  to about  $5 \times 10^6$ , about  $5 \times 10^6$  to about  $1 \times 10^7$ , about  $1 \times 10^6$  to about  $3 \times 10^6$ , about  $2 \times 10^6$  to about  $4 \times 10^6$ , about  $3 \times 10^6$  to about  $5 \times 10^6$ , about  $4 \times 10^6$  to about  $6 \times 10^6$ , about  $5 \times 10^6$  to about  $7 \times 10^6$ , about  $6 \times 10^6$  to about  $8 \times 10^6$ , about  $7 \times 10^6$  to about  $9 \times 10^6$ , about  $8 \times 10^6$  to about  $1 \times 10^7$ , about  $1 \times 10^6$  to about  $2 \times 10^6$ , about  $3 \times 10^6$  to about  $4 \times 10^6$ , about  $5 \times 10^6$  to about  $6 \times 10^6$ , about  $7 \times 10^6$  to about  $8 \times 10^6$ , about  $9 \times 10^6$  to about  $1 \times 10^7$ , or about  $1 \times 10^8$ ) viable CAR-positive cells (e.g., BCMA CAR+ T cells);
- (b) the second dose comprises about  $1 \times 10^7$  to about  $1 \times 10^8$  (e.g., about  $2 \times 10^7$  to about  $8 \times 10^7$ , about  $4 \times 10^7$  to about  $6 \times 10^7$ , about  $1 \times 10^7$  to about  $5 \times 10^7$ , about  $5 \times 10^7$  to about  $1 \times 10^8$ , about  $1 \times 10^7$  to about  $3 \times 10^7$ , about  $2 \times 10^7$  to about  $4 \times 10^7$ , about  $3 \times 10^7$  to about  $5 \times 10^7$ , about  $4 \times 10^7$  to about  $6 \times 10^7$ , about  $5 \times 10^7$  to about  $7 \times 10^7$ , about  $6 \times 10^7$  to about  $8 \times 10^7$ , about  $7 \times 10^7$  to about  $9 \times 10^7$ , about  $8 \times 10^7$  to about  $1 \times 10^8$ ) viable CAR-positive cells (e.g., BCMA CAR+ T cells);

- $9 \times 10^7$ , about  $8 \times 10^7$  to about  $1 \times 10^8$ , about  $1 \times 10^7$ , about  $2 \times 10^7$ , about  $3 \times 10^7$ , about  $4 \times 10^7$ , about  $5 \times 10^7$ , about  $6 \times 10^7$ , about  $7 \times 10^7$ , about  $8 \times 10^7$ , about  $9 \times 10^7$ , or about  $1 \times 10^8$ ) CAR-positive viable cells (e.g., BCMA CAR+ T cells);
- (c) the number of CAR-positive viable cells (e.g., BCMA CAR+ T cells) in the first dose is no more than  $1/X$ , wherein X is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100, of the number of CAR-positive viable cells (e.g., BCMA CAR+ T cells) in the second dose; and/or
- (d) the number of CAR-positive viable cells (e.g., BCMA CAR+ T cells) in the first dose is between about 1% and 100% (e.g., between about 10% and about 90%, between about 20% and about 80%, between about 30% and about 70%, between about 40% and about 60%, between about 10% and about 50%, between about 50% and about 90%, between about 10% and about 30%, between about 20% and about 40%, between about 30% and about 50%, between about 50% and about 70%, between about 60% and about 80%, or between about 70% and about 90%) of the number of CAR-positive viable cells (e.g., BCMA CAR+ T cells) in the second dose.

In some embodiments, the first dose comprises about  $5 \times 10^6$  viable CAR-positive cells (e.g., BCMA CAR+ T cells). In some embodiments, the second dose comprises about  $1 \times 10^7$  or about  $2 \times 10^7$  viable CAR-positive cells (e.g., BCMA CAR+ T cells).

In some embodiments, the method further comprises administering to the subject a second therapeutic agent. In some embodiments, the second therapeutic agent is chosen from: (i) a PD-1 inhibitor, optionally wherein the PD-1 inhibitor is selected from the group consisting of PDR001, Nivolumab, Pembrolizumab, Pidilizumab, MEDIO680, REGN2810, TSR-042, PF-06801591, and AMP-224; (ii) a PD-L1 inhibitor, optionally wherein the PD-L1 inhibitor is selected from the group consisting of FAZ053, Atezolizumab, Avelumab, Durvalumab, and BMS-936559; (iii) a LAG-3 inhibitor, optionally wherein the LAG-3 inhibitor is selected from the group consisting of LAG525, BMS-986016, TSR-033, MK-4280 and REGN3767; (iv) a TIM-3 inhibitor, optionally wherein the TIM-3 inhibitor is selected from the group consisting of MBG453, TSR-022, and LY3321367; (v) a CTLA-4 inhibitor, optionally wherein the CTLA-4 inhibitor is Ipilimumab or Tremelimumab; (vi) an interleukin-15 (IL-15) polypeptide, an interleukin-15 receptor alpha (IL-15Ra) polypeptide, or a combination of both an IL-15 polypeptide and an IL-15Ra polypeptide, e.g., hetIL-15; (vii) an interleukin-12 (IL-12) polypeptide; or (viii) an mTOR inhibitor, optionally wherein the mTOR inhibitor is RAD001 or rapamycin.

In some embodiments, provided herein is a cell comprising: (a) a first CAR comprising a first antigen-binding domain that binds to a first antigen, a first transmembrane domain, and a first intracellular signaling domain (e.g., a first primary signaling domain and/or a first costimulatory signaling domain), optionally wherein the first CAR further comprises a first leader sequence and/or a first hinge region; and (b) a second CAR comprising a second antigen-binding domain that binds to a second antigen, a second transmembrane domain, and a second intracellular signaling domain (e.g., a second primary signaling domain and/or a second costimulatory signaling domain), optionally wherein the second CAR further comprises a second leader sequence and/or a second hinge region, wherein: (i) the first leader sequence and the second leader sequence are encoded by

- different nucleic acid sequences (e.g., differ by at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, or 100%), optionally wherein the first and second leader sequences comprise the same amino acid sequence; (ii) the first hinge region and the second hinge region are encoded by different nucleic acid sequences (e.g., differ by at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, or 100%), optionally wherein the first and second hinge regions comprise the same amino acid sequence; (iii) the first transmembrane domain and the second transmembrane domain are encoded by different nucleic acid sequences (e.g., differ by at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, or 100%), optionally wherein the first and second transmembrane domains comprise the same amino acid sequence; and/or (iv) the first intracellular signaling domain and the second intracellular signaling domain are encoded by different nucleic acid sequences (e.g., differ by at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, or 100%), optionally wherein the first primary signaling domain and the second primary signaling domain are encoded by different nucleic acid sequences (e.g., differ by at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, or 100%), and/or the first costimulatory signaling domain and the second costimulatory signaling domain are encoded by different nucleic acid sequences (e.g., differ by at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, or 100%).

In some embodiments, provided herein is a nucleic acid molecule comprising: (a) a first nucleic acid sequence encoding a first CAR, wherein the first CAR comprises a first antigen-binding domain that binds to a first antigen, a first transmembrane domain, and a first intracellular signaling domain (e.g., a first primary signaling domain and/or a first costimulatory signaling domain), optionally wherein the first CAR further comprises a first leader sequence and/or a first hinge region; and (b) a second nucleic acid sequence encoding a second CAR, wherein the second CAR comprises a second antigen-binding domain that binds to a second antigen, a second transmembrane domain, and a second intracellular signaling domain (e.g., a second primary signaling domain and/or a second costimulatory signaling domain), optionally wherein the second CAR further comprises a second leader sequence and/or a second hinge region, wherein: (i) the first leader sequence and the second leader sequence are encoded by different nucleic acid sequences (e.g., differ by at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, or 100%), optionally wherein the first and second leader sequences comprise the same amino acid sequence; (ii) the first hinge region and the second hinge region are encoded by different nucleic acid sequences (e.g., differ by at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, or 100%), optionally wherein the first and second hinge regions comprise the same amino acid sequence; (iii) the first transmembrane domain and the second transmembrane domain are encoded by different nucleic acid sequences (e.g., differ by at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, or 100%), optionally wherein the first and second transmembrane domains comprise the same amino acid sequence; and/or (iv) the first intracellular signaling domain and the second intracellular signaling domain are encoded by different nucleic acid sequences (e.g., differ by at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, or 100%), optionally wherein the first intracellular signaling domain and the second intracellular signaling domain comprise the same amino acid sequence.

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In some embodiments, the first and second leader sequences comprise the same amino acid sequence. Without wishing to be bound by theory, such a nucleic acid molecule exhibits less recombination than an otherwise similar nucleic acid molecule in which the first leader sequence and the second leader sequence are encoded by the same nucleic acid sequence.

In some embodiments, the first and second hinge regions comprise the same amino acid sequence. Without wishing to be bound by theory, such a nucleic acid molecule exhibits less recombination than an otherwise similar nucleic acid molecule in which the first hinge region and the second hinge region are encoded by the same nucleic acid sequence.

In some embodiments, the first and second transmembrane domains comprise the same amino acid sequence. Without wishing to be bound by theory, such a nucleic acid molecule exhibits less recombination than an otherwise similar nucleic acid molecule in which the first transmembrane domain and the second transmembrane domain are encoded by the same nucleic acid sequence.

In some embodiments, the first intracellular signaling domain and the second intracellular signaling domain comprise the same amino acid sequence. Without wishing to be bound by theory, such a nucleic acid molecule exhibits less recombination than an otherwise similar nucleic acid molecule in which the first intracellular signaling domain and the second intracellular signaling domain are encoded by the same nucleic acid sequence.

In some embodiments, the first primary signaling domain and the second primary signaling domain comprise the same amino acid sequence. Without wishing to be bound by theory, such a nucleic acid molecule exhibits less recombination than an otherwise similar nucleic acid molecule in which the first primary signaling domain and the second primary signaling domain are encoded by the same nucleic acid sequence.

In some embodiments, the first primary signaling domain and the second primary signaling domain comprise different amino acid sequences.

In some embodiments, the first costimulatory signaling domain and the second costimulatory signaling domain comprise the same amino acid sequence. Without wishing to be bound by theory, such a nucleic acid molecule exhibits less recombination than an otherwise similar nucleic acid molecule in which the first costimulatory signaling domain and the second costimulatory signaling domain are encoded by the same nucleic acid sequence.

In some embodiments, the first costimulatory signaling domain and the second costimulatory signaling domain comprise different amino acid sequences (e.g., the first and second costimulatory signaling domains comprise a 4-1BB costimulatory domain sequence and a CD28 costimulatory domain sequence, respectively; or comprise a CD28 costimulatory domain sequence and a 4-1BB costimulatory domain sequence, respectively).

In some embodiments, the first leader sequence and the second leader sequence comprise the amino acid sequence of SEQ ID NO: 1, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the first leader sequence and the second leader sequence are encoded by nucleic acid sequences comprising SEQ ID NOs: 199 and 210, respectively (or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto), or SEQ ID NOs: 210 and 199, respectively (or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto).

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In some embodiments, the first hinge region and the second hinge region comprise the amino acid sequence of SEQ ID NO: 2, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the first hinge region and the second hinge region are encoded by nucleic acid sequences comprising SEQ ID NOs: 337 and 13, respectively (or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto); or SEQ ID NOs: 13 and 337, respectively (or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto).

In some embodiments, the first transmembrane domain and the second transmembrane domain comprise the amino acid sequence of SEQ ID NO: 6, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the first transmembrane domain and the second transmembrane domain are encoded by nucleic acid sequences comprising SEQ ID NOs: 338 and 17, respectively (or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto); or SEQ ID NOs: 17 and 338, respectively (or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto).

In some embodiments, the first costimulatory signaling domain and the second costimulatory signaling domain comprise the amino acid sequence of SEQ ID NO: 7, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the first costimulatory signaling domain and the second costimulatory signaling domain are encoded by nucleic acid sequences comprising SEQ ID NOs: 204 and 18, respectively (or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto); or SEQ ID NOs: 18 and 204, respectively (or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto).

In some embodiments, the first primary signaling domain and the second primary signaling domain comprise the amino acid sequence of SEQ ID NO: 10, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the first primary signaling domain and the second primary signaling domain are encoded by nucleic acid sequences comprising SEQ ID NOs: 205 and 21, respectively (or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto); or SEQ ID NOs: 21 and 205, respectively (or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto).

In some embodiments, the first and second antigens are different. In some embodiments, the first or second antigen is chosen from: BCMA, CD19, CDS, CD10, CD20, CD21, CD22, CD23, CD24, CD25, CD27, CD30, CD34, CD37, CD38, CD40, CD53, CD69, CD72, CD73, CD74, CD75, CD77, CD79a, CD79b, CD80, CD81, CD82, CD83, CD84, CD85, CD86, CD123, CD135, CD138, CD179, CD269, Flt3, ROR1, FcRn5, FcRn2, CS-1, CXCR4, 5, 7, IL-7/3R, IL7/4/3R, or IL4R, optionally wherein the B cell antigen is chosen from CD19, CD20, CD22, FcRn5, FcRn2, CS-1, CD138, CD123, CD33, CD34, CLL-1, folate receptor beta, FLT3, EGFRvIII, mesothelin, GD2, Tn antigen, sTn antigen, Tn-O-Glycopeptides, sTn-O-Glycopeptides, PSMA, CD97, TAG72, CD44v6, CEA, EPCAM, KIT, IL-13Ra2, leguman, GD3, CD171, IL-11Ra, PSCA, MAD-CT-1, MAD-CT-2, VEGFR2, LewisY, CD24, PDGFR-beta, SSEA-4, folate receptor alpha, ERBBs (e.g., ERBB2), Her2/neu, MUC1, EGFR, NCAM, Ephrin B2, CAIX, LMP2, sLe, HMWMAA, o-acetyl-GD2, folate receptor beta, TEM1/CD248, TEM7R,

FAP, Legumain, HPV E6 or E7, ML-IAP, CLDN6, TSHR, GPRC5D, ALK, Polysialic acid, Fos-related antigen, neutrophil elastase, TRP-2, CYP1B1, sperm protein 17, beta human chorionic gonadotropin, AFP, thyroglobulin, PLAC1, globoH, RAGE1, MN-CA IX, human telomerase reverse transcriptase, intestinal carboxyl esterase, mut hsp 70-2, NA-17, NY-BR-1, UPK2, HAVCR1, ADRB3, PANX3, NY-ESO-1, GPR20, Ly6k, OR51E2, TARP, GFR $\alpha$ 4, or a peptide of any of these antigens presented on MHC. In some embodiments, the first or second antigen-binding domain comprises a CDR, VH, VL, or scFv disclosed herein, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.

In some embodiments, provided herein is a CAR comprising a first VH (VH1), a first VL (VL1), a second VH (VH2), a second VL (VL2), a transmembrane domain, and an intracellular signaling domain, wherein the VH1 and VL1 bind to a first antigen and the VH2 and VL2 bind to a second antigen. In some embodiments, the VH1, VL1, VH2, and VL2 are arranged in the following configuration from the N-terminus to the C-terminus: VH1-optionally linker 1 ("L1")-VH2-optionally linker 2 ("L2")-VL2-optionally linker 3 ("L3")-VL1. In some embodiments, the VH1, VL1, VH2, and VL2 are arranged in the following configuration from the N-terminus to the C-terminus: VH1-optionally L1-VL2-optionally L2-VH2-optionally L3-VL1. In some embodiments, the VH1, VL1, VH2, and VL2 are arranged in the following configuration from the N-terminus to the C-terminus: VL1-optionally L1-VH2-optionally L2-VL2-optionally L3-VH1. In some embodiments, the VH1, VL1, VH2, and VL2 are arranged in the following configuration from the N-terminus to the C-terminus: VL1-optionally L1-VL2-optionally L2-VH2-optionally L3-VH1. In some embodiments, the VH1, VL1, VH2, and VL2 are arranged in the following configuration from the N-terminus to the C-terminus: VH2-optionally L1-VL1-optionally L2-VH1-optionally L3-VL2. In some embodiments, the VH1, VL1, VH2, and VL2 are arranged in the following configuration from the N-terminus to the C-terminus: VH2-optionally L2-VL1-optionally L1-VH1-optionally L2-VL1-optionally L3-VH2. In some embodiments, the VH1, VL1, VH2, and VL2 are arranged in the following configuration from the N-terminus to the C-terminus: VL2-optionally L1-VL1-optionally L2-VH1-optionally L3-VH2. In some embodiments, the VH1, VL1, VH2, and VL2 are arranged in the following configuration from the N-terminus to the C-terminus: VL2-optionally L1-VL1-optionally L2-VH1-optionally L3-VH2. In some embodiments, the VH1, VL1, VH2, and VL2 are arranged in the following configuration from the N-terminus to the C-terminus: VH1-linker 1 ("L1")-VH2-linker 2 ("L2")-VL2-linker 3 ("L3")-VL1. In some embodiments, the VH1, VL1, VH2, and VL2 are arranged in the following configuration from the N-terminus to the C-terminus: VH1-L1-VL2-L2-VH2-L3-VL1. In some embodiments, the VH1, VL1, VH2, and VL2 are arranged in the following configuration from the N-terminus to the C-terminus: VL1-L1-VL2-L2-VH2-L3-VH1. In some embodiments, the VH1, VL1, VH2, and VL2 are arranged in the following configuration from the N-terminus to the C-terminus: VH2-L1-VH1-L2-VL1-L3-VL2. In some embodiments, the VH1, VL1, VH2, and VL2 are arranged in the following configuration from the N-terminus to the C-terminus: VH2-L1-VL1-L2-VH1-L3-VL2. In some embodiments, the VH1, VL1, VH2, and VL2 are arranged in the following configuration from the N-terminus to the C-terminus: VL1-L1-VH1-L2-VL1-L3-VH2.

N-terminus to the C-terminus: VL2-L1-VH1-L2-VL1-L3-VH2. In some embodiments, the VH1, VL1, VH2, and VL2 are arranged in the following configuration from the N-terminus to the C-terminus: VL2-L1-VL1-L2-VH1-L3-VH2. In some embodiments, the L1 or L3 comprises the amino acid sequence of SEQ ID NO: 5, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the L2 comprises the amino acid sequence of SEQ ID NO: 63, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the CAR comprises the following configuration from the N-terminus to the C-terminus: (i) VH1-optionally linker 1 ("L1")-VH2-optionally linker 2 ("L2")-VL2-optionally linker 3 ("L3")-VL1-optionally a hinge region-transmembrane domain-intracellular signaling domain; (ii) VH1-optionally L1-VL2-optionally L2-VH2-optionally L3-VL1-optionally a hinge region-transmembrane domain-intracellular signaling domain; (iii) VL1-optionally L1-VH2-optionally L2-VL2-optionally L3-VH1-optionally a hinge region-transmembrane domain-intracellular signaling domain; (iv) VL1-optionally L1-VL2-optionally L2-VH2-optionally L3-VH1-optionally a hinge region-transmembrane domain-intracellular signaling domain; (v) VH2-optionally L1-VH1-optionally L2-VL1-optionally L3-VL2-optionally a hinge region-transmembrane domain-intracellular signaling domain; (vi) VH2-optionally L1-VL1-optionally L2-VH1-optionally L3-VL2-optionally a hinge region-transmembrane domain-intracellular signaling domain; (vii) VL2-optionally L1-VH1-optionally L2-VL1-optionally L3-VH2-optionally a hinge region-transmembrane domain-intracellular signaling domain; or (viii) VL2-optionally L1-VL1-optionally L2-VH1-optionally L3-VH2-optionally a hinge region-transmembrane domain-intracellular signaling domain. In some embodiments, the first and second antigens are different. In some embodiments, the first or second antigen is chosen from: BCMA, CD19, CD5, CD10, CD20, CD21, CD22, CD23, CD24, CD25, CD27, CD30, CD34, CD37, CD38, CD40, CD53, CD69, CD72, CD73, CD74, CD75, CD77, CD79a, CD79b, CD80, CD81, CD82, CD83, CD84, CD85, CD86, CD123, CD135, CD138, CD179, CD269, Flt3, ROR1, FcRn5, FcRn2, CS-1, CXCR4, 5, 7, IL-7/3R, IL-7/4/3R, or IL4R, optionally wherein the B cell antigen is chosen from CD19, CD20, CD22, FcRn5, FcRn2, CS-1, CD138, CD123, CD33, CD34, CLL-1, folate receptor beta, FLT3, EGFRvIII, mesothelin, GD2, Tn antigen, sTn antigen, Tn-O-Glycopeptides, sTn-O-Glycopeptides, PSMA, CD97, TAG72, CD44v6, CEA, EPCAM, KIT, IL-13Ra2, leguman, GD3, CD171, IL-11Ra, PSCA, MAD-CT-1, MAD-CT-2, VEGFR2, LewisY, CD24, PDGFR-beta, SSEA-4, folate receptor alpha, ERBBs (e.g., ERBB2), Her2/neu, MUC1, EGFR, NCAM, Ephrin B2, CAIX, LMP2, sLe, HMWMAA, o-acetyl-GD2, folate receptor beta, TEM1/CD248, TEM7R, FAP, Legumain, HPV E6 or E7, ML-IAP, CLDN6, TSHR, GPRC5D, ALK, Polysialic acid, Fos-related antigen, neutrophil elastase, TRP-2, CYP1B1, sperm protein 17, beta human chorionic gonadotropin, AFP, thyroglobulin, PLAC1, globoH, RAGE1, MN-CA IX, human telomerase reverse transcriptase, intestinal carboxyl esterase, mut hsp 70-2, NA-17, NY-BR-1, UPK2, HAVCR1, ADRB3, PANX3, NY-ESO-1, GPR20, Ly6k, OR51E2, TARP, GFR $\alpha$ 4, or a peptide of any of these antigens presented on MHC. In some embodiments, the VH1, VL1, VH2, or VL2 comprises a CDR, VH, or VL sequence disclosed herein, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the hinge region, transmembrane

domain, or intracellular signaling domain (e.g., a primary signaling domain and/or a costimulatory signaling domain) comprises a hinge region sequence, transmembrane domain sequence, or intracellular signaling domain sequence (e.g., a primary signaling domain sequence and/or a costimulatory signaling domain sequence) disclosed herein, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.

In some embodiments, provided herein is a nucleic acid molecule encoding a diabody CAR disclosed herein. In some embodiments, provided herein is a vector comprising a nucleic acid molecule encoding a diabody CAR disclosed herein. In some embodiments, provided herein is a cell comprising a CAR disclosed herein, a nucleic acid molecule encoding a diabody CAR disclosed herein, or a vector comprising a nucleic acid molecule encoding a diabody CAR disclosed herein. In some embodiments, provided herein is a pharmaceutical composition comprising a cell comprising a diabody CAR disclosed herein and a pharmaceutically acceptable carrier. In some embodiments, disclosed herein is a method of making a cell comprising a diabody CAR disclosed herein. In some embodiments, disclosed herein is a method of treating a subject, e.g., a subject having cancer, using a cell comprising a diabody CAR disclosed herein.

In some embodiments, the present disclosure pertains to methods of making immune effector cells (for example, T cells or NK cells) engineered to express a CAR, and compositions generated using such methods. The methods disclosed herein (e.g., the ARM process or the cytokine process disclosed herein) can be used to make cells expressing dual CARs or diabody CARs disclosed herein. Also disclosed are methods of using such compositions for treating a disease, for example, cancer, in a subject.

In some embodiments, this invention features a method of making a population of cells (for example, T cells) that express a chimeric antigen receptor (CAR), the method comprising: (i) contacting (for example, binding) a population of cells (for example, T cells, for example, T cells isolated from a frozen or fresh leukapheresis product) with an agent that stimulates a CD3/TCR complex and/or an agent that stimulates a costimulatory molecule on the surface of the cells; (ii) contacting the population of cells (for example, T cells) with a nucleic acid molecule (for example, a DNA or RNA molecule) encoding the CAR, thereby providing a population of cells (for example, T cells) comprising the nucleic acid molecule, and (iii) harvesting the population of cells (for example, T cells) for storage (for example, reformulating the population of cells in cryopreservation media) or administration, wherein: (a) step (ii) is performed together with step (i) or no later than 20 hours after the beginning of step (i), for example, no later than 12, 13, 14, 15, 16, 17, or 18 hours after the beginning of step (i), for example, no later than 18 hours after the beginning of step (i), and step (iii) is performed no later than 26 hours after the beginning of step (i), for example, no later than 22, 23, 24, or 25 hours after the beginning of step (i), for example, no later than 24 hours after the beginning of step (i); (b) step (ii) is performed together with step (i) or no later than 20 hours after the beginning of step (i), for example, no later than 12, 13, 14, 15, 16, 17, or 18 hours after the beginning of step (i), for example, no later than 18 hours after the beginning of step (i), and step (iii) is performed no later than 30 hours after the beginning of step (ii), for example, no later than 22, 23, 24, 25, 26, 27, 28, 29, or 30 hours after the beginning of step (ii); or (c) the population of cells from step (iii) are not expanded, or expanded by no

more than 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, or 40%, for example, no more than 10%, for example, as assessed by the number of living cells, compared to the population of cells at the beginning of step (i).  
5 In some embodiments, the nucleic acid molecule in step (ii) is a DNA molecule. In some embodiments, the nucleic acid molecule in step (ii) is an RNA molecule. In some embodiments, the nucleic acid molecule in step (ii) is on a viral vector, for example, a viral vector chosen from a lentivirus  
10 vector, an adenoviral vector, or a retrovirus vector. In some embodiments, the nucleic acid molecule in step (ii) is on a non-viral vector. In some embodiments, the nucleic acid molecule in step (ii) is on a plasmid. In some embodiments, the nucleic acid molecule in step (ii) is not on any vector. In  
15 some embodiments, step (ii) comprises transducing the population of cells (for example, T cells) with a viral vector comprising a nucleic acid molecule encoding the CAR. In some embodiments, step (ii) is performed together with step (i). In some embodiments, step (ii) is performed no later than  
20 20 hours after the beginning of step (i). In some embodiments, step (ii) is performed no later than 12, 13, 14, 15, 16, 17, or 18 hours after the beginning of step (i). In some embodiments, step (ii) is performed no later than 18 hours after the beginning of step (i). In some embodiments, step  
25 (iii) is performed no later than 26 hours after the beginning of step (i). In some embodiments, step (iii) is performed no later than 22, 23, 24, or 25 hours after the beginning of step (i). In some embodiments, step (iii) is performed no later than 24 hours after the beginning of step (i). In some  
30 embodiments, step (iii) is performed no later than 30 hours after the beginning of step (ii). In some embodiments, step (iii) is performed no later than 22, 23, 24, 25, 26, 27, 28, 29, or 30 hours after the beginning of step (ii). In some embodiments, the nucleic acid molecule encoding the CAR is a  
35 nucleic acid molecule disclosed herein. In some embodiments, the nucleic acid molecule comprises a first nucleic acid sequence encoding a first CAR and a second nucleic acid sequence encoding a second CAR. In some embodiments, the first and second nucleic acid sequences are  
40 disposed on a single nucleic acid molecule, e.g., wherein the first nucleic acid sequence and the second nucleic acid sequence are separated by a third nucleic acid sequence encoding a self-cleavage site (e.g., a P2A site, a T2A site, an E2A site, or an F2A site). In some embodiments, the first and  
45 second nucleic acid sequences are disposed on separate nucleic acid molecules. In some embodiments, the nucleic acid molecule comprises a nucleic acid sequence encoding a CAR, wherein the CAR comprises a first VH (VH1), a first VL (VL1), a second VH (VH2), a second VL (VL2), a  
50 transmembrane domain, and an intracellular signalling domain, wherein the VH1 ad VL1 bind to a first antigen and the VH2 and VL2 bind to a second antigen, wherein the VH1, VL1, VH2, and VL2 are arranged in the following configuration from the N-terminus to the C-terminus: VH1-  
55 optionally linker 1 (“L1”)-VH2-optional linker 2 (“L2”)-VL2-optional linker 3 (“L3”)-VL1, VH1-optional L1-VL2-optional L2-VH2-optional L3-VL1, VL1-optional L1-VH2-optional L2-VL2-optional L3-VH1,  
60 VL1-optional L1-VL2-optional L2-VH2-optional L3-VH1, VH2-optional L1-VH1-optional L2-VL1-optional L3-VL2, VH2-optional L1-VL1-optional L2-VH1-optional L3-VL2, VL2-optional L1-VH1-optional L2-VL1-optional L3-VH2; or VL2-optional L1-VL1-optional L2-VH1-optional L3-VH2.

65 In some embodiments, the population of cells from step (iii) are not expanded. In some embodiments, the population of cells from step (iii) are expanded by no more than 5, 6,

7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, or 40%, for example, as assessed by the number of living cells, compared to the population of cells at the beginning of step (i). In some embodiments, the population of cells from step (iii) are expanded by no more than 10%, for example, as assessed by the number of living cells, compared to the population of cells at the beginning of step (i).

In some embodiments, the nucleic acid molecule comprises a first nucleic acid sequence encoding a first CAR and a second nucleic acid sequence encoding a second CAR, wherein the first and second nucleic acid sequences are disposed on separate nucleic acid molecules.

In some embodiments, the first and second nucleic acid molecules are on separate viral vectors, and wherein step (ii) comprises transducing the population of cells (for example, T cells) with a first viral vector comprising the nucleic acid molecule encoding the first CAR and a second viral vector comprising the second nucleic acid molecule encoding the second CAR.

In some embodiments, the first CAR comprises an anti-BCMA binding domain (e.g., an anti-BCMA CAR) and the second CAR comprises an anti-CD19 binding domain (e.g., an anti-CD19 CAR).

In some embodiments, in step (ii), the population of cells is contacted with the first viral vector at a multiplicity of infection (MOI) that is higher than, equal to, or less than an MOI at which the population of cells is contacted with the second viral vector. In some embodiments, in step (ii), the population of cells is contacted with the first viral vector at a multiplicity of infection (MOI) that is higher than an MOI at which the population of cells is contacted with the second viral vector.

In some embodiments, in step (ii), the population of cells is contacted with the first viral vector at a first MOI and with the second viral vector at a second MOI, such that a resultant population of cells comprises a first population of cells that comprise the anti-BCMA CAR but not the anti-CD19 CAR, a second population of cells that comprise the anti-CD19 CAR but not the anti-BCMA CAR, and a third population of cells that comprise both the anti-BCMA CAR and the anti-CD19 CAR, wherein:

- (a) the total number of viable cells in the second and third populations combined is less than or equal to about 110% (e.g., less than or equal to about 105%, 100%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, 5%, 1%, or less) of the total number of viable cells in the first and third populations combined, e.g., as determined by a method described in Example 10;
- (b) the total number of viable cells in the first and third populations combined is greater than or equal to about 90% (e.g., greater than or equal to about 100%, 125%, 150%, 175%, 200%, 250%, 300%, 400%, 500%, 750%, 1000%, 2000%, 5000, 10000% or more) of the total number of viable cells in the second and third populations combined, e.g., as determined by a method described in Example 10;
- (c) the total number of viable cells in the first and third populations combined is greater than or equal to about 5% (e.g., greater than or equal to about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90%) of the total number of viable cells in the resultant population, e.g., as determined by a method described in Example 10;
- (d) the total number of viable cells in the second population is less than or equal to about 110% (e.g., less than or equal to about 105%, 100%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, 5%, 1%, or less) of the total number of viable cells in the first and third populations combined, e.g., as determined by a method described in Example 10;

populations combined, e.g., as determined by a method described in Example 10; or

(e) the total number of viable cells in the first and third populations combined is greater than or equal to about 90% (e.g., greater than or equal to about 100%, 125%, 150%, 175%, 200%, 250%, 300%, 400%, 500%, 750%, 1000%, 2000%, 5000, 10000% or more) of the total number of viable cells in the second population, e.g., as determined by a method described in Example 10. In some embodiments, in step (ii), the population of cells is contacted with the second viral vector at an MOI (e.g., an MOI that is sufficiently lower than an MOI at which the population of cells is contacted with the first viral vector, such that in a resultant population of cells:

- (a) the total number of viable cells in the second and third populations combined is less than or equal to about 110% (e.g., less than or equal to about 105%, 100%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, 5%, 1%, or less) of the total number of viable cells in the first and third populations combined, e.g., as determined by a method described in Example 10;
- (b) the total number of viable cells in the first and third populations combined is greater than or equal to about 90% (e.g., greater than or equal to about 100%, 125%, 150%, 175%, 200%, 250%, 300%, 400%, 500%, 750%, 1000%, 2000%, 5000, 10000% or more) of the total number of viable cells in the second and third populations combined, e.g., as determined by a method described in Example 10;
- (c) the total number of viable cells in the first and third populations combined is greater than or equal to about 5% (e.g., greater than or equal to about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90%) of the total number of viable cells in the resultant population, e.g., as determined by a method described in Example 10;
- (d) the total number of viable cells in the second population is less than or equal to about 110% (e.g., less than or equal to about 105%, 100%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, 5%, 1%, or less) of the total number of viable cells in the first and third populations combined, e.g., as determined by a method described in Example 10; or
- (e) the total number of viable cells in the first and third populations combined is greater than or equal to about 90% (e.g., greater than or equal to about 100%, 125%, 150%, 175%, 200%, 250%, 300%, 400%, 500%, 750%, 1000%, 2000%, 5000, 10000% or more) of the total number of viable cells in the second population, e.g., as determined by a method described in Example 10.

In some embodiments, in step (ii), the population of cells is contacted with the first viral vector at a first MOI, and the population of cells is contacted with the second viral vector at a second MOI, such that a resultant population of cells comprises:

- (a) the total number of viable cells in the second and third populations combined is less than or equal to about 110% (e.g., less than or equal to about 105%, 100%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, 5%, 1%, or less) of the total number of viable cells in the first and third populations combined, e.g., as determined by a method described in Example 10;
- (b) the total number of viable cells in the first and third populations combined is greater than or equal to about 90% (e.g., greater than or equal to about 100%, 125%, 150%, 175%, 200%, 250%, 300%, 400%, 500%,

- 750%, 1000%, 2000%, 5000, 10000% or more) of the total number of viable cells in the second and third populations combined, e.g., as determined by a method described in Example 10;
- (c) the total number of viable cells in the first and third populations combined is greater than or equal to about 5% (e.g., greater than or equal to about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90%) of the total number of viable cells in the resultant population, e.g., as determined by a method described in Example 10;
- (d) the total number of viable cells in the second population is less than or equal to about 110% (e.g., less than or equal to about 105%, 100%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, 5%, 1%, or less) of the total number of viable cells in the first and third populations combined, e.g., as determined by a method described in Example 10; or
- (e) the total number of viable cells in the first and third populations combined is greater than or equal to about 90% (e.g., greater than or equal to about 100%, 125%, 150%, 175%, 200%, 250%, 300%, 400%, 500%, 750%, 1000%, 2000%, 5000, 10000% or more) of the total number of viable cells in the second population, e.g., as determined by a method described in Example 10.

In some embodiments, in step (ii), the population of cells is contacted with:

- (a) the first viral vector at an MOI of about 1 to about 10 (e.g., about 2 to about 9, about 3 to about 8, about 4 to about 7, about 5 to about 6, about 1 to about 8, about 1 to about 6, about 1 to about 4, about 8 to about 10, about 6 to about 10, about 4 to about 10, about 1 to about 3, about 2 to about 4, about 3 to about 5, about 4 to about 6, about 5 to about 7, about 6 to about 8, about 7 to about 9, about 8 to about 10, about 2.5 to about 5, about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, or about 10);
- (b) the second viral vector at an MOI of about 0.1 to about 5 (e.g., about 0.2 to about 4, about 0.3 to about 3, about 0.4 to about 2, about 0.5 to about 1, about 0.6 to about 0.9, about 0.7 to about 0.8, about 0.1 to about 4, about 0.1 to about 3, about 0.1 to about 2, about 0.1 to about 1, about 0.1 to about 0.5, about 4 to about 5, about 3 to about 5, about 2 to about 5, about 1 to about 5, about 0.5 to about 5, about 0.2 to about 5, about 0.1 to about 0.5, about 0.2 to about 1, about 0.5 to about 2, about 1 to about 3, about 2 to about 4, about 3 to about 5, about 0.5 to about 1, about 0.1, about 0.2, about 0.3, about 0.4, about 0.5, about 0.6, about 0.7, about 0.8, about 0.9, about 1, about 2, about 3, about 4, or about 5);
- (c) the first viral vector at an MOI that is at least about 10% (e.g., at least about 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90%) or at least about 1 fold (e.g., at least about 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, or 100 fold, e.g., about 2 to about 50 fold, about 3 to 20 fold, about 5 to about 15 fold, or about 8 to about 10 fold) higher than an MOI at which the population of cells is contacted with the second viral vector; and/or
- (d) the second viral vector at an MOI that is no more than 1/X, wherein X is 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 20, 30, 40, 50, 60, 70, 80, 90, or 100, of an MOI at which the population of cells is contacted with the first viral vector.

In some embodiments, the population of cells is contacted with the first viral vector at an MOI of about 2.5 to about 5. In some embodiments, the population of cells is contacted

with the second viral vector at an MOI of about 0.5 to about 1.0. In some embodiments, the first viral vector at an MOI that is about 8 to about 10 fold higher than an MOI at which the population of cells is contacted with the second viral vector. In some embodiments, the second viral vector at an MOI that is no more than 1/X, wherein X is 6, 8, 10, or 12, of an MOI at which the population of cells is contacted with the first viral vector.

In some embodiments, in step (ii), the population of cells is contacted with:

- (a) the first viral vector at an MOI of between about 4 and about 5 (e.g., about 4.75); and/or
- (b) the second viral vector at an MOI between about 0.2 and about 1 (e.g., about 0.5).

In some embodiments, in step (ii), the population of cells comprises about  $1 \times 10^8$  to about  $5 \times 10^9$  (e.g., about  $2 \times 10^8$  to about  $2 \times 10^9$  or about  $4 \times 10^8$  to about  $1 \times 10^9$ ) total viable cells. In some embodiments, the cells are suspended in a culture at a concentration of about  $1 \times 10^6$  to about  $1 \times 10^7$  (e.g., about  $2 \times 10^6$  to about  $5 \times 10^6$  or about  $3 \times 10^6$  to about  $4 \times 10^6$ ) viable cells/mL.

In some embodiments, the agent that stimulates a CD3/TCR complex is an agent that stimulates CD3. In some embodiments, the agent that stimulates a costimulatory molecule is an agent that stimulates CD28, ICOS, CD27, HVEM, LIGHT, CD40, 4-1BB, OX40, DR3, GITR, CD30, TIM1, CD2, CD226, or any combination thereof. In some embodiments, the agent that stimulates a costimulatory molecule is an agent that stimulates CD28. In some embodiments, the agent that stimulates a CD3/TCR complex is chosen from an antibody (for example, a single-domain antibody (for example, a heavy chain variable domain antibody), a peptibody, a Fab fragment, or a scFv), a small molecule, or a ligand (for example, a naturally-existing, recombinant, or chimeric ligand). In some embodiments, the agent that stimulates a costimulatory molecule is chosen from an antibody (for example, a single-domain antibody (for example, a heavy chain variable domain antibody), a peptibody, a Fab fragment, or a scFv), a small molecule, or a ligand (for example, a naturally-existing, recombinant, or chimeric ligand). In some embodiments, the agent that stimulates a CD3/TCR complex does not comprise a bead. In some embodiments, the agent that stimulates a costimulatory molecule does not comprise a bead. In some embodiments, the agent that stimulates a CD3/TCR complex comprises an anti-CD3 antibody. In some embodiments, the agent that stimulates a costimulatory molecule comprises an anti-CD28 antibody. In some embodiments, the agent that stimulates a CD3/TCR complex comprises an anti-CD3 antibody covalently attached to a colloidal polymeric nanomatrix. In some embodiments, the agent that stimulates a costimulatory molecule comprises an anti-CD28 antibody covalently attached to a colloidal polymeric nanomatrix. In some embodiments, the agent that stimulates a CD3/TCR complex and the agent that stimulates a costimulatory molecule comprise T Cell TransAct™.

In some embodiments, the agent that stimulates a CD3/TCR complex does not comprise hydrogel. In some embodiments, the agent that stimulates a costimulatory molecule does not comprise hydrogel. In some embodiments, the agent that stimulates a CD3/TCR complex does not comprise alginate. In some embodiments, the agent that stimulates a costimulatory molecule does not comprise alginate.

In some embodiments, the agent that stimulates a CD3/TCR complex comprises hydrogel. In some embodiments, the agent that stimulates a costimulatory molecule comprises hydrogel. In some embodiments, the agent that stimulates a

CD3/TCR complex comprises alginate. In some embodiments, the agent that stimulates a costimulatory molecule comprises alginate. In some embodiments, the agent that stimulates a CD3/TCR complex or the agent that stimulates a costimulatory molecule comprises MagCloudz™ from Quad Technologies.

In some embodiments, step (i) increases the percentage of CAR-expressing cells in the population of cells from step (iii), for example, the population of cells from step (iii) shows a higher percentage of CAR-expressing cells (for example, at least 10, 20, 30, 40, 50, or 60% higher), compared with cells made by an otherwise similar method without step (i).

In some embodiments, the percentage of naïve cells, for example, naïve T cells, for example, CD45RA+CD45RO-CCR7+ T cells, in the population of cells from step (iii) is the same as the percentage of naïve cells, for example, naïve T cells, for example, CD45RA+CD45RO-CCR7+ cells, in the population of cells at the beginning of step (i). In some embodiments, the percentage of naïve cells, for example, naïve T cells, for example, CD45RA+CD45RO-CCR7+ T cells, in the population of cells from step (iii) differs by no more than 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12% from the percentage of naïve cells, for example, naïve T cells, for example, CD45RA+CD45RO-CCR7+ cells, in the population of cells at the beginning of step (i). In some embodiments, the percentage of naïve cells, for example, naïve T cells, for example, CD45RA+CD45RO-CCR7+ T cells, in the population of cells from step (iii) differs by no more than 5 or 10% from the percentage of naïve cells, for example, naïve T cells, for example, CD45RA+CD45RO-CCR7+ cells, in the population of cells at the beginning of step (i).

In some embodiments, the population of cells from step (iii) shows a higher percentage of naïve cells, for example, naïve T cells, for example, CD45RA+CD45RO-CCR7+ T cells (for example, at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, or 40% higher), compared with cells made by an otherwise similar method in which step (iii) is performed more than 26 hours after the beginning of step (i), for example, more than 5, 6, 7, 8, 9, 10, 11, or 12 days after the beginning of step (i). In some embodiments, the population of cells from step (iii) shows a higher percentage of naïve cells, for example, naïve T cells, for example, CD45RA+CD45RO-CCR7+ T cells (for example, at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, or 40% higher), compared with cells made by an otherwise similar method which further comprises, after step (ii) and prior to step (iii), expanding the population of cells (for example, T cells) in vitro for more than 3 days, for example, for 5, 6, 7, 8 or 9 days.

In some embodiments, the percentage of central memory cells, for example, central memory T cells, for example, CD95+ central memory T cells, in the population of cells from step (iii) is the same as the percentage of central memory cells, for example, central memory T cells, for example, CD95+ central memory T cells, in the population of cells at the beginning of step (i). In some embodiments, the percentage of central memory cells, for example, central memory T cells, for example, CD95+ central memory T cells, in the population of cells from step (iii) differs by no more than 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12% from the percentage of central memory cells, for example, central memory T cells, for example, CD95+ central memory T cells, in the population of cells at the beginning of step (i). In some embodiments, the percentage of central memory cells, for example, central memory T cells, for example, CD95+ central memory T cells, in the population of cells from step (iii) differs by no more than 5, 6, 7, 8, 9, 10, 11, or 12 days after the beginning of step (i).

from step (iii) differs by no more than 5 or 10% from the percentage of central memory cells, for example, central memory T cells, for example, CD95+ central memory T cells, in the population of cells at the beginning of step (i).

In some embodiments, the population of cells from step (iii) shows a lower percentage of central memory cells, for example, central memory T cells, for example, CD95+ central memory T cells (for example, at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, or 40% lower), compared with cells made by an otherwise similar method in which step (iii) is performed more than 26 hours after the beginning of step (i), for example, more than 5, 6, 7, 8, 9, 10, 11, or 12 days after the beginning of step (i). In some embodiments, the population of cells from step (iii) shows a lower percentage of central memory cells, for example, central memory T cells, for example, CD95+ central memory T cells (for example, at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, or 40% lower), compared with cells made by an otherwise similar method which further comprises, after step (ii) and prior to step (iii), expanding the population of cells (for example, T cells) in vitro for more than 3 days, for example, for 5, 6, 7, 8 or 9 days.

In some embodiments, the percentage of stem memory T cells, for example, CD45RA+CD95+IL-2 receptor β+CCR7+CD62L+ T cells, in the population of cells from step (iii) is increased, as compared to the percentage of stem memory T cells, for example, CD45RA+CD95+IL-2 receptor β+CCR7+CD62L+ T cells, in the population of cells at the beginning of step (i). In some embodiments, the percentage of CAR-expressing stem memory T cells, for example, CAR-expressing CD45RA+CD95+IL-2 receptor β+CCR7+CD62L+ T cells, in the population of cells from step (iii) is increased, as compared to the percentage of CAR-expressing stem memory T cells, for example, CAR-expressing CD45RA+CD95+IL-2 receptor β+CCR7+CD62L+ T cells, in the population of cells at the beginning of step (i). In some embodiments, the percentage of stem memory T cells, for example, CD45RA+CD95+IL-2 receptor β+CCR7+CD62L+ T cells, in the population of cells from step (iii) is higher than the percentage of stem memory T cells, for example, CD45RA+CD95+IL-2 receptor β+CCR7+CD62L+ T cells, in cells made by an otherwise similar method in which step (iii) is performed more than 26 hours after the beginning of step (i), for example, more than 5, 6, 7, 8, 9, 10, 11, or 12 days after the beginning of step (i). In some embodiments, the percentage of CAR-expressing stem memory T cells, for example, CAR-expressing CD45RA+CD95+IL-2 receptor β+CCR7+CD62L+ T cells, in the population of cells from step (iii) is higher than the percentage of CAR-expressing stem memory T cells, for example, CAR-expressing CD45RA+CD95+IL-2 receptor β+CCR7+CD62L+ T cells, in cells made by an otherwise similar method in which step (iii) is performed more than 26 hours after the beginning of step (i), for example, more than 5, 6, 7, 8, 9, 10, 11, or 12 days after the beginning of step (i). In some embodiments, the percentage of stem memory T cells, for example, CD45RA+CD95+IL-2 receptor β+CCR7+CD62L+ T cells, in the population of cells from step (iii) is higher than the percentage of stem memory T cells, for example, CD45RA+CD95+IL-2 receptor β+CCR7+CD62L+ T cells, in cells made by an otherwise similar method which further comprises, after step (ii) and prior to step (iii), expanding the population of cells (for example, T cells) in vitro for more than 3 days, for example, for 5, 6, 7, 8 or 9 days. In some embodiments, the percentage of CAR-expressing stem memory T cells, for example, CAR-expressing CD45RA+CD95+IL-2 receptor β+CCR7+

CD62L+ T cells, in the population of cells from step (iii) is higher than the percentage of CAR-expressing stem memory T cells, for example, CAR-expressing CD45RA+CD95+ IL-2 receptor  $\beta$ +CCR7+CD62L+ T cells, in cells made by an otherwise similar method which further comprises, after step (ii) and prior to step (iii), expanding the population of cells (for example, T cells) in vitro for more than 3 days, for example, for 5, 6, 7, 8 or 9 days.

In some embodiments, the median GeneSetScore (Up TEM vs. Down TSCM) of the population of cells from step (iii) is about the same as or differs by no more than (for example, increased by no more than) about 25, 50, 75, 100, or 125% from the median GeneSetScore (Up TEM vs. Down TSCM) of the population of cells at the beginning of step (i). In some embodiments, the median GeneSetScore (Up TEM vs. Down TSCM) of the population of cells from step (iii) is lower (for example, at least about 100, 150, 200, 250, or 300% lower) than the median GeneSetScore (Up TEM vs. Down TSCM) of cells made by an otherwise similar method in which step (iii) is performed more than 26 hours after the beginning of step (i), for example, more than 5, 6, 7, 8, 9, 10, 11, or 12 days after the beginning of step (i). In some embodiments, the median GeneSetScore (Up TEM vs. Down TSCM) of the population of cells from step (iii) is lower (for example, at least about 100, 150, 200, 250, or 300% lower) than the median GeneSetScore (Up TEM vs. Down TSCM) of cells made by an otherwise similar method which further comprises, after step (ii) and prior to step (iii), expanding the population of cells (for example, T cells) in vitro for more than 3 days, for example, for 5, 6, 7, 8 or 9 days. In some embodiments, the median GeneSetScore (Up Treg vs. Down Teff) of the population of cells from step (iii) is about the same as or differs by no more than (for example, increased by no more than) about 25, 50, 100, 150, or 200% from the median GeneSetScore (Up Treg vs. Down Teff) of the population of cells at the beginning of step (i). In some embodiments, the median GeneSetScore (Up Treg vs. Down Teff) of the population of cells from step (iii) is lower (for example, at least about 50, 100, 125, 150, or 175% lower) than the median GeneSetScore (Up Treg vs. Down Teff) of cells made by an otherwise similar method in which step (iii) is performed more than 26 hours after the beginning of step (i), for example, more than 5, 6, 7, 8, 9, 10, 11, or 12 days after the beginning of step (i). In some embodiments, the median GeneSetScore (Up Treg vs. Down Teff) of the population of cells from step (iii) is lower (for example, at least about 50, 100, 125, 150, or 175% lower) than the median GeneSetScore (Up Treg vs. Down Teff) of cells made by an otherwise similar method which further comprises, after step (ii) and prior to step (iii), expanding the population of cells (for example, T cells) in vitro for more than 3 days, for example, for 5, 6, 7, 8 or 9 days. In some embodiments, the median GeneSetScore (Down stemness) of the population of cells from step (iii) is about the same as or differs by no more than (for example, increased by no more than) about 25, 50, 100, 150, 200, or 250% from the median GeneSetScore (Down stemness) of the population of cells at the beginning of step (i). In some embodiments, the median GeneSetScore (Down stemness) of the population of cells from step (iii) is lower (for example, at least about 50, 100, or 125% lower) than the median GeneSetScore (Down stemness) of cells made by an otherwise similar method in which step (iii) is performed more than 26 hours after the beginning of step (i), for example, more than 5, 6, 7, 8, 9, 10, 11, or 12 days after the beginning of step (i). In some embodiments, the median GeneSetScore (Down stemness) of the population of cells from step (iii) is lower (for example, at least about 50, 100, or 125% lower) than the median GeneSetScore (Down stemness) of cells made by an otherwise similar method which further comprises, after step (ii) and prior to step (iii), expanding the population of cells (for example, T cells) in vitro for more than 3 days, for example, for 5, 6, 7, 8 or 9 days.

example, at least about 50, 100, or 125% lower) than the median GeneSetScore (Down stemness) of cells made by an otherwise similar method which further comprises, after step (ii) and prior to step (iii), expanding the population of cells (for example, T cells) in vitro for more than 3 days, for example, for 5, 6, 7, 8 or 9 days. In some embodiments, the median GeneSetScore (Up hypoxia) of the population of cells from step (iii) is about the same as or differs by no more than (for example, increased by no more than) about 125, 150, 175, or 200% from the median GeneSetScore (Up hypoxia) of the population of cells at the beginning of step (i). In some embodiments, the median GeneSetScore (Up hypoxia) of the population of cells from step (iii) is lower (for example, at least about 40, 50, 60, 70, or 80% lower) than the median GeneSetScore (Up hypoxia) of cells made by an otherwise similar method in which step (iii) is performed more than 26 hours after the beginning of step (i), for example, more than 5, 6, 7, 8, 9, 10, 11, or 12 days after the beginning of step (i). In some embodiments, the median GeneSetScore (Up hypoxia) of the population of cells from step (iii) is lower (for example, at least about 40, 50, 60, 70, or 80% lower) than the median GeneSetScore (Up hypoxia) of cells made by an otherwise similar method which further comprises, after step (ii) and prior to step (iii), expanding the population of cells (for example, T cells) in vitro for more than 3 days, for example, for 5, 6, 7, 8 or 9 days. In some embodiments, the median GeneSetScore (Up autophagy) of the population of cells from step (iii) is about the same as or differs by no more than (for example, increased by no more than) about 180, 190, 200, or 210% from the median GeneSetScore (Up autophagy) of the population of cells at the beginning of step (i). In some embodiments, the median GeneSetScore (Up autophagy) of the population of cells from step (iii) is lower (for example, at least 20, 30, or 40% lower) than the median GeneSetScore (Up autophagy) of cells made by an otherwise similar method in which step (iii) is performed more than 26 hours after the beginning of step (i), for example, more than 5, 6, 7, 8, 9, 10, 11, or 12 days after the beginning of step (i). In some embodiments, the median GeneSetScore (Up autophagy) of the population of cells from step (iii) is lower (for example, at least 20, 30, or 40% lower) than the median GeneSetScore (Up autophagy) of cells made by an otherwise similar method which further comprises, after step (ii) and prior to step (iii), expanding the population of cells (for example, T cells) in vitro for more than 3 days, for example, for 5, 6, 7, 8 or 9 days.

In some embodiments, the population of cells from step (iii), after being incubated with a cell expressing an antigen recognized by the CAR, secretes IL-2 at a higher level (for example, at least 2, 4, 6, 8, 10, 12, or 14-fold higher) than cells made by an otherwise similar method in which step (iii) is performed more than 26 hours after the beginning of step (i), for example, more than 5, 6, 7, 8, 9, 10, 11, or 12 days after the beginning of step (i), or cells made by an otherwise similar method which further comprises, after step (ii) and prior to step (iii), expanding the population of cells (for example, T cells) in vitro for more than 3 days, for example, for 5, 6, 7, 8 or 9 days.

In some embodiments, the population of cells from step (iii), after being administered *in vivo*, persists longer or expands at a higher level (for example, at least 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, or 90% higher), compared with cells made by an otherwise similar method in which step (iii) is performed more than 26 hours after the beginning of step (i), for example, more than 5, 6, 7, 8, 9, 10, 11, or 12 days after the beginning of step (i). In some embodiments, the population of cells from step (iii), after

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being administered in vivo, persists longer or expands at a higher level (for example, at least 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, or 90% higher), compared with cells made by an otherwise similar method which further comprises, after step (ii) and prior to step (iii), expanding the population of cells (for example, T cells) in vitro for more than 3 days, for example, for 5, 6, 7, 8 or 9 days.

In some embodiments, the population of cells from step (iii), after being administered in vivo, shows a stronger anti-tumor activity (for example, a stronger anti-tumor activity at a low dose, for example, a dose no more than  $0.15 \times 10^6$ ,  $0.2 \times 10^6$ ,  $0.25 \times 10^6$ , or  $0.3 \times 10^6$  viable CAR-expressing cells) than cells made by an otherwise similar method in which step (iii) is performed more than 26 hours after the beginning of step (i), for example, more than 5, 6, 7, 8, 9, 10, 11, or 12 days after the beginning of step (i), or cells made by an otherwise similar method which further comprises, after step (ii) and prior to step (iii), expanding the population of cells (for example, T cells) in vitro for more than 3 days, for example, for 5, 6, 7, 8 or 9 days.

In some embodiments, the population of cells from step (iii) are not expanded, for example, as assessed by the number of living cells, compared to the population of cells at the beginning of step (i). In some embodiments, the population of cells from step (iii) decreases from the number of living cells in the population of cells at the beginning of step (i), for example, as assessed by the number of living cells. In some embodiments, the population of cells from step (iii) are expanded by no more than 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, or 40%, for example, no more than 10%, for example, as assessed by the number of living cells, compared to the population of cells at the beginning of step (i). In some embodiments, the population of cells from step (iii) are not expanded, or expanded by less than 0.5, 1, 1.5, or 2 hours, for example, less than 1 or 1.5 hours, compared to the population of cells at the beginning of step (i).

In some embodiments, steps (i) and (ii) are performed in cell media (for example, serum-free media) comprising IL-2, IL-15 (for example, hetIL-15 (IL15/sIL-15Ra)), IL-6 (for example, IL-6/sIL-6Ra), a LSD1 inhibitor, or a MALT1 inhibitor. In some embodiments, steps (i) and (ii) are performed in cell media (for example, serum-free media) comprising IL-7, IL-21, or a combination thereof. In some embodiments, steps (i) and (ii) are performed in cell media (for example, serum-free media) comprising IL-2, IL-15 (for example, hetIL-15 (IL15/sIL-15Ra)), IL-6 (for example, IL-6/sIL-6Ra), a LSD1 inhibitor, or a MALT1 inhibitor. In some embodiments, step (ii) is performed in cell media (for example, serum-free media) comprising IL-2, IL-15 (for example, hetIL-15 (IL15/sIL-15Ra)), IL-6 (for example, IL-6/sIL-6Ra), a LSD1 inhibitor, or a MALT1 inhibitor. In some embodiments, step (i) is performed in cell media (for example, serum-free media) comprising IL-2, IL-15 (for example, hetIL-15 (IL15/sIL-15Ra)), IL-6 (for example, IL-6/sIL-6Ra), a LSD1 inhibitor, or a MALT1 inhibitor. In some embodiments, step (i) is performed in cell media (for example, serum-free media) comprising IL-7, IL-21, or a combination thereof. In some embodiments, step (ii) is performed in cell media (for example, serum-free media) comprising IL-7, IL-21, or a combination thereof. In some embodiments, step (i) is performed in cell media (for example, serum-free media) comprising IL-2, IL-15 (for example, hetIL-15 (IL15/sIL-15Ra)), IL-21, IL-7, IL-6 (for example, IL-6/sIL-6Ra), a LSD1 inhibitor, a MALT1 inhibitor, or a combination thereof. In some embodiments, step (ii) is performed in cell media (for example, serum-free media) comprising IL-2, IL-15 (for example, hetIL-15 (IL15/sIL-15Ra)), IL-21, IL-7, IL-6 (for example, IL-6/sIL-6Ra), a LSD1 inhibitor, a MALT1 inhibitor, or a combination thereof. In some embodiments, step (i) is performed in cell media (for example, serum-free media) comprising IL-2, IL-15 (for example, hetIL-15 (IL15/sIL-15Ra)), IL-21, IL-7, IL-6 (for example, IL-6/sIL-6Ra), a LSD1 inhibitor, a MALT1 inhibitor, or a combination thereof. In some embodiments, step (ii) is performed in cell

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media (for example, serum-free media) comprising IL-2, IL-15 (for example, hetIL-15 (IL15/sIL-15Ra)), IL-21, IL-7, IL-6 (for example, IL-6/sIL-6Ra), a LSD1 inhibitor, a MALT1 inhibitor, or a combination thereof. In some embodiments, the cell media is a serum-free media comprising a serum replacement. In some embodiments, the serum replacement is CTSTM Immune Cell Serum Replacement (ICSR).

In some embodiments, the aforementioned methods further comprise prior to step (i): (iv) receiving a fresh leukapheresis product (or an alternative source of hematopoietic tissue such as a fresh whole blood product, a fresh bone marrow product, or a fresh tumor or organ biopsy or removal (for example, a fresh product from thymectomy)) from an entity, for example, a laboratory, hospital, or healthcare provider.

In some embodiments, the aforementioned methods further comprise prior to step (i): (v) isolating the population of cells (for example, T cells, for example, CD8+ and/or CD4+ T cells) contacted in step (i) from a fresh leukapheresis product (or an alternative source of hematopoietic tissue such as a fresh whole blood product, a fresh bone marrow product, or a fresh tumor or organ biopsy or removal (for example, a fresh product from thymectomy)). In some embodiments, step (iii) is performed no later than 35 hours after the beginning of step (v), for example, no later than 27, 28, 29, 30, 31, 32, 33, 34, or 35 hours after the beginning of step (v), for example, no later than 30 hours after the beginning of step (v). In some embodiments, the population of cells from step (iii) are not expanded, or expanded by no more than 5, 10, 15, 20, 25, 30, 35, or 40%, for example, no more than 10%, for example, as assessed by the number of living cells, compared to the population of cells at the end of step (v).

In some embodiments, the aforementioned methods further comprise prior to step (i): receiving cryopreserved T cells isolated from a leukapheresis product (or an alternative source of hematopoietic tissue such as cryopreserved T cells isolated from whole blood, bone marrow, or tumor or organ biopsy or removal (for example, thymectomy)) from an entity, for example, a laboratory, hospital, or healthcare provider.

In some embodiments, the aforementioned methods further comprise prior to step (i): (iv) receiving a cryopreserved leukapheresis product (or an alternative source of hematopoietic tissue such as a cryopreserved whole blood product, a cryopreserved bone marrow product, or a cryopreserved tumor or organ biopsy or removal (for example, a cryopreserved product from thymectomy)) from an entity, for example, a laboratory, hospital, or healthcare provider.

In some embodiments, the aforementioned methods further comprise prior to step (i): (v) isolating the population of cells (for example, T cells, for example, CD8+ and/or CD4+ T cells) contacted in step (i) from a cryopreserved leukapheresis product (or an alternative source of hematopoietic tissue such as a cryopreserved whole blood product, a cryopreserved bone marrow product, or a cryopreserved tumor or organ biopsy or removal (for example, a cryopreserved product from thymectomy)). In some embodiments, step (iii) is performed no later than 35 hours after the beginning of step (v), for example, no later than 27, 28, 29, 30, 31, 32, 33, 34, or 35 hours after the beginning of step (v), for example, no later than 30 hours after the beginning of step (v). In some embodiments, the population of cells from step (iii) are not expanded, or expanded by no more than 5, 10, 15, 20, 25, 30, 35, or 40%, for example, no more than

10%, for example, as assessed by the number of living cells, compared to the population of cells at the end of step (v).

In some embodiments, the cells from step (iii) are cultured for about two to about four days, e.g., about three days (e.g., about 72 hours following harvesting) prior to measuring CAR expression level in the portion (for example, measuring the percentage of viable, CAR-expressing cells in the portion, for example, measuring the percentage of viable, anti-BCMA CAR-expressing cells in the portion). In some embodiments, the measuring of CAR expression occurs about 4 days (e.g., 96 hours) after step (ii). In some embodiments, the CAR expression level is measured by flow cytometry.

In some embodiments, this invention features a method of making a population of cells (for example, T cells) that express a chimeric antigen receptor (CAR), the method comprising: (1) contacting a population of cells (for example, T cells, for example, T cells isolated from a frozen leukapheresis product) with a cytokine chosen from IL-2, IL-7, IL-15, IL-21, IL-6, or a combination thereof, (2) contacting the population of cells (for example, T cells) with a nucleic acid molecule (for example, a DNA or RNA molecule) encoding the CAR, thereby providing a population of cells (for example, T cells) comprising the nucleic acid molecule, and (3) harvesting the population of cells (for example, T cells) for storage (for example, reformulating the population of cells in cryopreservation media) or administration, wherein: (a) step (2) is performed together with step (1) or no later than 5 hours after the beginning of step (1), for example, no later than 1, 2, 3, 4, or 5 hours after the beginning of step (1), and step (3) is performed no later than 26 hours after the beginning of step (1), for example, no later than 22, 23, 24, or 25 hours after the beginning of step (1), for example, no later than 24 hours after the beginning of step (1), or (b) the population of cells from step (3) are not expanded, or expanded by no more than 5, 10, 15, 20, 25, 30, 35, or 40%, for example, no more than 10%, for example, as assessed by the number of living cells, compared to the population of cells at the beginning of step (1). In some embodiments, the nucleic acid molecule in step (2) is a DNA molecule. In some embodiments, the nucleic acid molecule in step (2) is an RNA molecule. In some embodiments, the nucleic acid molecule in step (2) is on a viral vector, for example, a viral vector chosen from a lentivirus vector, an adenoviral vector, or a retrovirus vector. In some embodiments, the nucleic acid molecule in step (2) is on a non-viral vector. In some embodiments, the nucleic acid molecule in step (2) is on a plasmid. In some embodiments, the nucleic acid molecule in step (2) is not on any vector. In some embodiments, step (2) comprises transducing the population of cells (for example, T cells) with a viral vector comprising a nucleic acid molecule encoding the CAR. In some embodiments, the nucleic acid molecule encoding the CAR is a nucleic acid molecule disclosed herein. In some embodiments, the nucleic acid molecule comprises a first nucleic acid sequence encoding a first CAR and a second nucleic acid sequence encoding a second CAR. In some embodiments, the first and second nucleic acid sequences are disposed on a single nucleic acid molecule, e.g., wherein the first nucleic acid sequence and the second nucleic acid sequence are separated by a third nucleic acid sequence encoding a self-cleavage site (e.g., a P2A site, a T2A site, an E2A site, or an F2A site). In some embodiments, the first and second nucleic acid sequences are disposed on separate nucleic acid molecules. In some embodiments, the nucleic acid molecule comprises a nucleic acid sequence encoding a CAR, wherein the CAR comprises a first VH (VH1), a first

VL (VL1), a second VH (VH2), a second VL (VL2), a transmembrane domain, and an intracellular signaling domain, wherein the VH1 and VL1 bind to a first antigen and the VH2 and VL2 bind to a second antigen, wherein the VH1, VL1, VH2, and VL2 are arranged in the following configuration from the N-terminus to the C-terminus: VH1-optional linker 1 ("L1")-VH2-optional linker 2 ("L2")-VL2-optional linker 3 ("L3")-VL1, VH1-optional L1-VL2-optional L2-VH2-optional L3-VL1, VL1-optional L1-VH2-optional L2-VL2-optional L3-VH1, VL1-optional L1-VL2-optional L2-VH2-optional L3-VH1, VH2-optional L1-VH1-optional L2-VL1-optional L3-VL2, VH2-optional L1-VL1-optional L2-VH1-optional L3-VL2, VL2-optional L1-VH1-optional L2-VL1-optional L3-VH2; or VL2-optional L1-VL1-optional L2-VH1-optional L3-VH2.

In some embodiments, step (2) is performed together with step (1). In some embodiments, step (2) is performed no later than 5 hours after the beginning of step (1). In some embodiments, step (2) is performed no later than 1, 2, 3, 4, or 5 hours after the beginning of step (1). In some embodiments, step (3) is performed no later than 26 hours after the beginning of step (1). In some embodiments, step (3) is performed no later than 22, 23, 24, or 25 hours after the beginning of step (1). In some embodiments, step (3) is performed no later than 24 hours after the beginning of step (1).

In some embodiments, the population of cells from step (3) are not expanded, for example, as assessed by the number of living cells, compared to the population of cells at the beginning of step (1). In some embodiments, the population of cells from step (3) are expanded by no more than 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, or 40%, for example, as assessed by the number of living cells, compared to the population of cells at the beginning of step (1). In some embodiments, the population of cells from step (3) are expanded by no more than 10%, for example, as assessed by the number of living cells, compared to the population of cells at the beginning of step (1).

In some embodiments, step (1) comprises contacting the population of cells (for example, T cells) with IL-2. In some embodiments, step (1) comprises contacting the population of cells (for example, T cells) with IL-7. In some embodiments, step (1) comprises contacting the population of cells (for example, T cells) with IL-15 (for example, hetIL-15 (IL15/sIL-15Ra)). In some embodiments, step (1) comprises contacting the population of cells (for example, T cells) with IL-21. In some embodiments, step (1) comprises contacting the population of cells (for example, T cells) with IL-6 (for example, IL-6/sIL-6Ra). In some embodiments, step (1) comprises contacting the population of cells (for example, T cells) with IL-2 and IL-7. In some embodiments, step (1) comprises contacting the population of cells (for example, T cells) with IL-2 and IL-15 (for example, hetIL-15 (IL15/sIL-15Ra)). In some embodiments, step (1) comprises contacting the population of cells (for example, T cells) with IL-2 and IL-21. In some embodiments, step (1) comprises contacting the population of cells (for example, T cells) with IL-2 and IL-6 (for example, IL-6/sIL-6Ra). In some embodiments, step (1) comprises contacting the population of cells (for example, T cells) with IL-7 and IL-15 (for example, hetIL-15 (IL15/sIL-15Ra)). In some embodiments, step (1) comprises contacting the population of cells (for example, T cells) with IL-7 and IL-21. In some embodiments, step (1) comprises contacting the population of cells (for example, T cells) with IL-7 and IL-6 (for example, IL-6/sIL-6Ra). In some embodiments, step (1) comprises contacting the popu-

lation of cells (for example, T cells) with IL-15 (for example, hetIL-15 (IL15/sIL-15Ra)) and IL-21. In some embodiments, step (1) comprises contacting the population of cells (for example, T cells) with IL-15 (for example, hetIL-15 (IL15/sIL-15Ra)) and IL-6 (for example, IL-6/sIL-6Ra). In some embodiments, step (1) comprises contacting the population of cells (for example, T cells) with IL-21 and IL-6 (for example, IL-6/sIL-6Ra). In some embodiments, step (1) comprises contacting the population of cells (for example, T cells) with IL-7, IL-15 (for example, hetIL-15 (IL15/sIL-15Ra)), and IL-21.

In some embodiments, the population of cells from step (3) shows a higher percentage of naïve cells among CAR-expressing cells (for example, at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, or 40% higher), compared with cells made by an otherwise similar method which further comprises contacting the population of cells with, for example, an anti-CD3 antibody.

In some embodiments, the percentage of naïve cells, for example, naïve T cells, for example, CD45RA+CD45RO-CCR7+ T cells, in the population of cells from step (3) is the same as the percentage of naïve cells, for example, naïve T cells, for example, CD45RA+CD45RO-CCR7+ cells, in the population of cells at the beginning of step (1). In some embodiments, the percentage of naïve cells, for example, naïve T cells, for example, CD45RA+CD45RO-CCR7+ T cells, in the population of cells from step (3) differs by no more than 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12% from the percentage of naïve cells, for example, naïve T cells, for example, CD45RA+CD45RO-CCR7+ cells, in the population of cells at the beginning of step (1). In some embodiments, the percentage of naïve cells, for example, naïve T cells, for example, CD45RA+CD45RO-CCR7+ T cells, in the population of cells from step (3) differs by no more than 5 or 10% from the percentage of naïve cells, for example, naïve T cells, for example, CD45RA+CD45RO-CCR7+ cells, in the population of cells at the beginning of step (1). In some embodiments, the percentage of naïve cells, for example, naïve T cells, for example, CD45RA+CD45RO-CCR7+ T cells, in the population of cells from step (3) is increased as compared to the percentage of naïve cells, for example, naïve T cells, for example, CD45RA+CD45RO-CCR7+ cells, in the population of cells at the beginning of step (1). In some embodiments, the percentage of naïve cells, for example, naïve T cells, for example, CD45RA+CD45RO-CCR7+ T cells, in the population of cells from step (3) is increased by at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20%, as compared to the percentage of naïve cells, for example, naïve T cells, for example, CD45RA+CD45RO-CCR7+ cells, in the population of cells at the beginning of step (1). In some embodiments, the percentage of naïve cells, for example, naïve T cells, for example, CD45RA+CD45RO-CCR7+ T cells, in the population of cells from step (3) is increased by at least 10 or 20%, as compared to the percentage of naïve cells, for example, naïve T cells, for example, CD45RA+CD45RO-CCR7+ T cells, in the population of cells at the beginning of step (1).

In some embodiments, the population of cells from step (3) shows a higher percentage of naïve cells, for example, naïve T cells, for example, CD45RA+CD45RO-CCR7+ T cells (for example, at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, or 40% higher), compared with cells made by an otherwise similar method in which step (3) is performed more than 26 hours after the beginning of step (1), for example, more than 5, 6, 7, 8, 9, 10, 11, or 12 days after the beginning of step (1). In some embodiments, the population of cells from step (3) shows a higher percentage of

naïve cells, for example, naïve T cells, for example, CD45RA+CD45RO-CCR7+ T cells (for example, at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, or 40% higher), compared with cells made by an otherwise similar method which further comprises, after step (2) and prior to step (3), expanding the population of cells (for example, T cells) in vitro for more than 3 days, for example, for 5, 6, 7, 8 or 9 days.

In some embodiments, the percentage of central memory cells, for example, central memory T cells, for example, CD95+ central memory T cells, in the population of cells from step (3) is the same as the percentage of central memory cells, for example, central memory T cells, for example, CD95+ central memory T cells, in the population of cells at the beginning of step (1). In some embodiments, the percentage of central memory cells, for example, central memory T cells, for example, CD95+ central memory T cells, in the population of cells from step (3) differs by no more than 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12% from the percentage of central memory cells, for example, central memory T cells, for example, CD95+ central memory T cells, in the population of cells at the beginning of step (1). In some embodiments, the percentage of central memory cells, for example, central memory T cells, for example, CD95+ central memory T cells, in the population of cells from step (3) differs by no more than 5 or 10% from the percentage of central memory cells, for example, central memory T cells, for example, CD95+ central memory T cells, in the population of cells at the beginning of step (1). In some embodiments, the percentage of central memory cells, for example, central memory T cells, for example, CD95+ central memory T cells, in the population of cells from step (3) is decreased as compared to the percentage of central memory cells, for example, central memory T cells, for example, CD95+ central memory T cells, in the population of cells at the beginning of step (1). In some embodiments, the percentage of central memory cells, for example, central memory T cells, for example, CD95+ central memory T cells, in the population of cells from step (3) is decreased by at least 10 or 20%, as compared to the percentage of central memory cells, for example, central memory T cells, for example, CD95+ central memory T cells, in the population of cells at the beginning of step (1). In some embodiments, the percentage of central memory cells, for example, central memory T cells, for example, CD95+ central memory T cells, in the population of cells from step (3) is decreased by at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20%, as compared to the percentage of central memory cells, for example, central memory T cells, for example, CD95+ central memory T cells, in the population of cells at the beginning of step (1).

In some embodiments, the population of cells from step (3) shows a lower percentage of central memory cells, for example, central memory T cells, for example, CD95+ central memory T cells (for example, at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, or 40% lower), compared with cells made by an otherwise similar method in which step (3) is performed more than 26 hours after the beginning of step (1), for example, more than 5, 6, 7, 8, 9, 10, 11, or 12 days after the beginning of step (1). In some embodiments, the population of cells from step (3) shows a lower percentage of central memory cells, for example, central memory T cells, for example, CD95+ central memory T cells (for example, at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, or 40% lower), compared with cells made by an otherwise similar method which further comprises, after step (2) and prior to step (3), expanding the

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population of cells (for example, T cells) in vitro for more than 3 days, for example, for 5, 6, 7, 8 or 9 days.

In some embodiments, the population of cells from step (3), after being administered in vivo, persists longer or expands at a higher level (for example, at least 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, or 90% higher), compared with cells made by an otherwise similar method in which step (3) is performed more than 26 hours after the beginning of step (1), for example, more than 5, 6, 7, 8, 9, 10, 11, or 12 days after the beginning of step (1). In some embodiments, the population of cells from step (3), after being administered in vivo, persists longer or expands at a higher level (for example, at least 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, or 90% higher), compared with cells made by an otherwise similar method which further comprises, after step (2) and prior to step (3), expanding the population of cells (for example, T cells) in vitro for more than 3 days, for example, for 5, 6, 7, 8 or 9 days.

In some embodiments, the population of cells from step (3) are not expanded, for example, as assessed by the number of living cells, compared to the population of cells at the beginning of step (1). In some embodiments, the population of cells from step (3) are expanded by no more than 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, or 40%, for example, as assessed by the number of living cells, compared to the population of cells at the beginning of step (1). In some embodiments, the population of cells from step (3) are expanded by no more than 10%, for example, as assessed by the number of living cells, compared to the population of cells at the beginning of step (1). In some embodiments, the number of living cells in the population of cells from step (3) decreases from the number of living cells in the population of cells at the beginning of step (1), for example, as assessed by the number of living cells.

In some embodiments, the population of cells from step (3) are not expanded compared to the population of cells at the beginning of step (1), for example, as assessed by the number of living cells. In some embodiments, the population of cells from step (3) are expanded by less than 0.5, 1, 1.5, or 2 hours, for example, less than 1 or 1.5 hours, compared to the population of cells at the beginning of step (1).

In some embodiments, the population of cells is not contacted in vitro with an agent that stimulates a CD3/TCR complex and/or an agent that stimulates a costimulatory molecule on the surface of the cells, or if contacted, the contacting step is less than 2 hours, for example, no more than 1 or 1.5 hours. In some embodiments, the agent that stimulates a CD3/TCR complex is an agent that stimulates CD3 (for example, an anti-CD3 antibody). In some embodiments, the agent that stimulates a costimulatory molecule is an agent that stimulates CD28, ICOS, CD27, HVEM, LIGHT, CD40, 4-1BB, OX40, DR3, GITR, CD30, TIM1, CD2, CD226, or any combination thereof. In some embodiments, the agent that stimulates a costimulatory molecule is an agent that stimulates CD28. In some embodiments, the agent that stimulates a CD3/TCR complex or the agent that stimulates a costimulatory molecule is chosen from an antibody (for example, a single-domain antibody (for example, a heavy chain variable domain antibody), a peptide antibody, a Fab fragment, or a scFv), a small molecule, or a ligand (for example, a naturally-existing, recombinant, or chimeric ligand).

In some embodiments, steps (1) and/or (2) are performed in cell media comprising no more than 5, 4, 3, 2, 1, or 0% serum. In some embodiments, steps (1) and/or (2) are performed in cell media comprising no more than 2% serum.

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In some embodiments, steps (1) and/or (2) are performed in cell media comprising about 2% serum. In some embodiments, steps (1) and/or (2) are performed in cell media comprising a LSD1 inhibitor or a MALT1 inhibitor. In some embodiments, step (1) is performed in cell media comprising no more than 5, 4, 3, 2, 1, or 0% serum. In some embodiments, step (1) is performed in cell media comprising no more than 2% serum. In some embodiments, step (1) is performed in cell media comprising about 2% serum. In some embodiments, step (2) is performed in cell media comprising no more than 5, 4, 3, 2, 1, or 0% serum. In some embodiments, step (2) is performed in cell media comprising no more than 2% serum. In some embodiments, step (2) is performed in cell media comprising a LSD1 inhibitor or a MALT1 inhibitor. In some embodiments, step (2) is performed in cell media comprising a LSD1 inhibitor or a MALT1 inhibitor.

In some embodiments, the aforementioned methods further comprise prior to step (i): (iv) receiving a fresh leukapheresis product (or an alternative source of hematopoietic tissue such as a fresh whole blood product, a fresh bone marrow product, or a fresh tumor or organ biopsy or removal (for example, a fresh product from thymectomy)) from an entity, for example, a laboratory, hospital, or healthcare provider.

In some embodiments, the aforementioned methods further comprise prior to step (i): (v) isolating the population of cells (for example, T cells, for example, CD8+ and/or CD4+ T cells) contacted in step (i) from a fresh leukapheresis product (or an alternative source of hematopoietic tissue such as a fresh whole blood product, a fresh bone marrow product, or a fresh tumor or organ biopsy or removal (for example, a fresh product from thymectomy)). In some embodiments, step (iii) is performed no later than 35 hours after the beginning of step (v), for example, no later than 27, 28, 29, 30, 31, 32, 33, 34, or 35 hours after the beginning of step (v), for example, no later than 30 hours after the beginning of step (v). In some embodiments, the population of cells from step (iii) are not expanded, or expanded by no more than 5, 10, 15, 20, 25, 30, 35, or 40%, for example, no more than 10%, for example, as assessed by the number of living cells, compared to the population of cells at the end of step (v).

In some embodiments, the aforementioned methods further comprise prior to step (i): receiving cryopreserved T cells isolated from a leukapheresis product (or an alternative source of hematopoietic tissue such as cryopreserved T cells isolated from whole blood, bone marrow, or tumor or organ biopsy or removal (for example, thymectomy)) from an entity, for example, a laboratory, hospital, or healthcare provider.

In some embodiments, the aforementioned methods further comprise prior to step (i): (iv) receiving a cryopreserved leukapheresis product (or an alternative source of hematopoietic tissue such as a cryopreserved whole blood product, a cryopreserved bone marrow product, or a cryopreserved tumor or organ biopsy or removal (for example, a cryopreserved product from thymectomy)) from an entity, for example, a laboratory, hospital, or healthcare provider.

In some embodiments, the aforementioned methods further comprise prior to step (i): (v) isolating the population of cells (for example, T cells, for example, CD8+ and/or CD4+ T cells) contacted in step (i) from a cryopreserved leukapheresis product (or an alternative source of hematopoietic tissue such as a cryopreserved whole blood product, a cryopreserved bone marrow product, or a cryopreserved

tumor or organ biopsy or removal (for example, a cryopreserved product from thymectomy)). In some embodiments, step (iii) is performed no later than 35 hours after the beginning of step (v), for example, no later than 27, 28, 29, 30, 31, 32, 33, 34, or 35 hours after the beginning of step (v), for example, no later than 30 hours after the beginning of step (v). In some embodiments, the population of cells from step (iii) are not expanded, or expanded by no more than 5, 10, 15, 20, 25, 30, 35, or 40%, for example, no more than 10%, for example, as assessed by the number of living cells, compared to the population of cells at the end of step (v).

In some embodiments, the population of cells at the beginning of step (i) or step (1) has been enriched for IL6R-expressing cells (for example, cells that are positive for IL6Ra and/or IL6R $\beta$ ). In some embodiments, the population of cells at the beginning of step (i) or step (1) comprises no less than 40, 45, 50, 55, 60, 65, or 70% of IL6R-expressing cells (for example, cells that are positive for IL6Ra and/or IL6R $\beta$ ).

In some embodiments, steps (i) and (ii) or steps (1) and (2) are performed in cell media comprising IL-15 (for example, hetIL-15 (IL15/sIL-15Ra)). In some embodiments, IL-15 increases the ability of the population of cells to expand, for example, 10, 15, 20, or 25 days later. In some embodiments, IL-15 increases the percentage of IL6R $\beta$ -expressing cells in the population of cells.

In some embodiments of the aforementioned methods, the methods are performed in a closed system. In some embodiments, T cell separation, activation, transduction, incubation, and washing are all performed in a closed system. In some embodiments of the aforementioned methods, the methods are performed in separate devices. In some embodiments, T cell separation, activation and transduction, incubation, and washing are performed in separate devices.

In some embodiments of the aforementioned methods, the methods further comprise adding an adjuvant or a transduction enhancement reagent in the cell culture medium to enhance transduction efficiency. In some embodiments, the adjuvant or transduction enhancement reagent comprises a cationic polymer. In some embodiments, the adjuvant or transduction enhancement reagent is chosen from: LentiBOOST™ (Sirion Biotech), vectofusin-1, F108, hexadimethrine bromide (Polybrene), PEA, Pluronic F68, Pluronic F127, Syneronic or LentiTrans™. In some embodiments, the adjuvant is LentiBOOST™ (Sirion Biotech).

In some embodiments of the aforementioned methods, the transducing the population of cells (for example, T cells) with a viral vector comprises subjecting the population of cells and viral vector to a centrifugal force under conditions such that transduction efficiency is enhanced. In an embodiment, the cells are transduced by spinoculation.

In some embodiments of the aforementioned methods, cells (e.g., T cells) are activated and transduced in a cell culture flask comprising a gas-permeable membrane at the base that supports large media volumes without substantially compromising gas exchange. In some embodiments, cell growth is achieved by providing access, e.g., substantially uninterrupted access, to nutrients through convection.

In some embodiments of the aforementioned methods, the CAR comprises an antigen binding domain, a transmembrane domain, and an intracellular signaling domain.

In some embodiments, the antigen binding domain binds to an antigen chosen from: CD19, CD20, CD22, BCMA, mesothelin, EGFRvIII, GD2, Tn antigen, sTn antigen, Tn-O-Glycopeptides, sTn-O-Glycopeptides, PSMA, CD97, TAG72, CD44v6, CEA, EPCAM, KIT, IL-13Ra2, leguman, GD3, CD171, IL-11Ra, PSCA, MAD-CT-1, MAD-CT-2,

VEGFR2, LewisY, CD24, PDGFR-beta, SSEA-4, folate receptor alpha, ERBBs (for example, ERBB2), Her2/neu, MUC1, EGFR, NCAM, Ephrin B2, CAIX, LMP2, sLe, HMWMAA, o-acetyl-GD2, folate receptor beta, TEM1/CD248, TEM7R, FAP, Legumain, HPV E6 or E7, ML-IAP, CLDN6, TSHR, GPRC5D, ALK, Polysialic acid, Fos-related antigen, neutrophil elastase, TRP-2, CYP1B1, sperm protein 17, beta human chorionic gonadotropin, AFP, thyroglobulin, PLAC1, globoH, RAGE1, MN-Ca IX, human telomerase reverse transcriptase, intestinal carboxyl esterase, mut hsp 70-2, NA-17, NY-BR-1, UPK2, HAVCR1, ADRB3, PANX3, NY-ESO-1, GPR20, Ly6k, OR51E2, TARP, GFR $\alpha$ 4, or a peptide of any of these antigens presented on MHC. In some embodiments, the antigen binding domain comprises a CDR, VH, VL, scFv or a CAR sequence disclosed herein. In some embodiments, the antigen binding domain comprises a VH and a VL, wherein the VH and VL are connected by a linker, optionally wherein the linker comprises the amino acid sequence of SEQ ID NO: 63 or 104.

In some embodiments, the transmembrane domain comprises a transmembrane domain of a protein chosen from the alpha, beta or zeta chain of T-cell receptor, CD28, CD3 epsilon, CD45, CD4, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137 and CD154. In some embodiments, the transmembrane domain comprises a transmembrane domain of CD8. In some embodiments, the transmembrane domain comprises the amino acid sequence of SEQ ID NO: 6, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereof. In some embodiments, the nucleic acid molecule comprises a nucleic acid sequence encoding the transmembrane domain, wherein the nucleic acid sequence comprises the nucleic acid sequence of SEQ ID NO: 17, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereof.

In some embodiments, the antigen binding domain is connected to the transmembrane domain by a hinge region. In some embodiments, the hinge region comprises the amino acid sequence of SEQ ID NO: 2, 3, or 4, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereof. In some embodiments, the nucleic acid molecule comprises a nucleic acid sequence encoding the hinge region, wherein the nucleic acid sequence comprises the nucleic acid sequence of SEQ ID NO: 13, 14, or 15, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereof.

In some embodiments, the intracellular signaling domain comprises a primary signaling domain. In some embodiments, the primary signaling domain comprises a functional signaling domain derived from CD3 zeta, TCR zeta, FcR gamma, FcR beta, CD3 gamma, CD3 delta, CD3 epsilon, CDS, CD22, CD79a, CD79b, CD278 (ICOS), Fc $\epsilon$ RI, DAP10, DAP12, or CD66d. In some embodiments, the primary signaling domain comprises a functional signaling domain derived from CD3 zeta. In some embodiments, the primary signaling domain comprises the amino acid sequence of SEQ ID NO: 9 or 10, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereof. In some embodiments, the nucleic acid molecule comprises a nucleic acid sequence encoding the primary signaling domain, wherein the nucleic acid sequence comprises the nucleic acid sequence of SEQ ID NO: 20 or 21, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereof.

In some embodiments, the intracellular signaling domain comprises a costimulatory signaling domain. In some

embodiments, the costimulatory signaling domain comprises a functional signaling domain derived from a MHC class I molecule, a TNF receptor protein, an Immunoglobulin-like protein, a cytokine receptor, an integrin, a signaling lymphocytic activation molecule (SLAM protein), an activating NK cell receptor, BTLA, a Toll ligand receptor, OX40, CD2, CD7, CD27, CD28, CD30, CD40, CDS, ICAM-1, 4-1BB (CD137), B7-H3, ICOS (CD278), GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMP7, NKP80 (KLRF1), NKP44, NKP30, NKP46, CD19, CD4, CD8alpha, CD8beta, IL2R beta, IL2R gamma, IL7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, ITGB7, NKG2D, NKG2C, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMP4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMP6 (NTB-A, Ly108), SLAM (SLAMP1, CD150, IPO-3), BLAME (SLAMP8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, CD28-OX40, CD28-4-1BB, or a ligand that specifically binds with CD83. In some embodiments, the costimulatory signaling domain comprises a functional signaling domain derived from 4-1BB. In some embodiments, the costimulatory signaling domain comprises the amino acid sequence of SEQ ID NO: 7, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereof. In some embodiments, the nucleic acid molecule comprises a nucleic acid sequence encoding the costimulatory signaling domain, wherein the nucleic acid sequence comprises the nucleic acid sequence of SEQ ID NO: 18, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereof.

In some embodiments, the intracellular signaling domain comprises a functional signaling domain derived from 4-1BB and a functional signaling domain derived from CD3 zeta. In some embodiments, the intracellular signaling domain comprises the amino acid sequence of SEQ ID NO: 7 (or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereof) and the amino acid sequence of SEQ ID NO: 9 or 10 (or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereof). In some embodiments, the intracellular signaling domain comprises the amino acid sequence of SEQ ID NO: 7 and the amino acid sequence of SEQ ID NO: 9 or 10.

In some embodiments, the CAR further comprises a leader sequence comprising the amino acid sequence of SEQ ID NO: 1.

In some embodiments, this invention features a population of CAR-expressing cells (for example, autologous or allogeneic CAR-expressing T cells or NK cells) made by any of the aforementioned methods or any other method disclosed herein. In some embodiments, disclosed herein is a pharmaceutical composition comprising a population of CAR-expressing cells disclosed herein and a pharmaceutically acceptable carrier.

In some embodiments, the population comprises:

- a first population of cells comprising an anti-BCMA CAR but not an anti-CD19 CAR;
- a second population of cells comprising an anti-CD19 CAR but not an anti-BCMA CAR; and
- a third population of cells comprising both an anti-BCMA CAR and an anti-CD19 CAR.

In some embodiments:

- the total number of viable cells in the second and third populations combined is less than or equal to about 110% (e.g., less than or equal to about 105%, 100%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, 5%, 1%, or less) of the total number of viable cells in the first and third populations combined;
- the total number of viable cells in the first and third populations combined is greater than or equal to about 90% (e.g., greater than or equal to about 100%, 125%, 150%, 175%, 200%, 250%, 300%, 400%, 500%, 750%, 1000%, 2000%, 5000, 10000% or more) of the total number of viable cells in the second and third populations combined; and/or
- the total number of viable cells in the first and third populations combined is greater than or equal to about 5% (e.g., greater than or equal to about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90%) of the total number of viable cells in the population.

In some embodiments, the population further comprises a fourth population of cells that do not comprise a CAR.

In some embodiments:

- the total number of viable cells in the second population is less than or equal to about 110% (e.g., less than or equal to about 105%, 100%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, 5%, 1%, or less) of the total number of viable cells in the first and third populations combined;
- the total number of viable cells in the second population is less than or equal to: about 45% to about 50% (e.g., about 47%); about 50 to about 55% (e.g., about 53%); about 60% to about 65% (e.g., about 63%); or about 80 to about 85% (e.g., about 82%) of the total number of viable cells in the first and third populations combined.

In some embodiments, in the final CAR cell product manufactured using the methods described herein, the total amount of beads (e.g., CD4 beads, CD8 beads, and/or TransACT beads) is no more than 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.1, 0.2, 0.3, 0.4, or 0.5% of the total amount of beads added during the manufacturing process.

In some embodiments, this invention features a population of CAR-expressing cells (for example, autologous or allogeneic CAR-expressing T cells or NK cells) comprising one or more of the following characteristics: (a) about the same percentage of naïve cells, for example, naïve T cells, for example, CD45RO-CCR7+ T cells, as compared to the percentage of naïve cells, for example, naïve T cells, for example, CD45RO-CCR7+ cells, in the same population of cells prior to being engineered to express the CAR; (b) a change within about 5% to about 10% of naïve cells, for example, naïve T cells, for example, CD45RO-CCR7+ T cells, for example, as compared to the percentage of naïve cells, for example, naïve T cells, for example, CD45RO-CCR7+ cells, in the same population of cells prior to being engineered to express the CAR; (c) an increased percentage of naïve cells, for example, naïve T cells, for example, CD45RO-CCR7+ T cells, for example, increased by at least 1.2, 1.4, 1.6, 1.8, 2.0, 2.2, 2.4, 2.6, 2.8, or 3-fold, as compared to the percentage of naïve cells, for example, naïve T cells, for example, CD45RO-CCR7+ cells, in the same population of cells prior to being engineered to express the CAR; (d) about the same percentage of central memory cells, for example, central memory T cells, for example, CCR7+CD45RO+ T cells, as compared to the percentage of central memory cells, for example, central memory T cells, for example, CCR7+CD45RO+ T cells, in the same population of cells prior to being engineered to express the CAR;

(e) a change within about 5% to about 10% of central memory cells, for example, central memory T cells, for example, CCR7+CD45RO+ T cells, as compared to the percentage of central memory cells, for example, central memory T cells, for example, CCR7+CD45RO+ T cells, in the same population of cells prior to being engineered to express the CAR; (f) a decreased percentage of central memory cells, for example, central memory T cells, for example, CCR7+CD45RO+ T cells, decreased by at least 20, 25, 30, 35, 40, 45, or 50%, as compared to the percentage of central memory cells, for example, central memory T cells, for example, CCR7+CD45RO+ T cells, in the same population of cells prior to being engineered to express the CAR; (g) about the same percentage of stem memory T cells, for example, CD45RA+CD95+IL-2 receptor  $\beta$ +CCR7+CD62L+ T cells, as compared to the percentage of stem memory T cells, for example, CD45RA+CD95+IL-2 receptor  $\beta$ +CCR7+CD62L+ T cells, in the same population of cells prior to being engineered to express the CAR; (h) a change within about 5% to about 10% of stem memory T cells, for example, CD45RA+CD95+IL-2 receptor  $\beta$ +CCR7+CD62L+ T cells, as compared to the percentage of stem memory T cells, for example, CD45RA+CD95+IL-2 receptor  $\beta$ +CCR7+CD62L+ T cells, in the same population of cells prior to being engineered to express the CAR; or (i) an increased percentage of stem memory T cells, for example, CD45RA+CD95+IL-2 receptor  $\beta$ +CCR7+CD62L+ T cells, as compared to the percentage of stem memory T cells, for example, CD45RA+CD95+IL-2 receptor  $\beta$ +CCR7+CD62L+ T cells, in the same population of cells prior to being engineered to express the CAR.

In some embodiments, this invention features a population of CAR-expressing cells (for example, autologous or allogeneic CAR-expressing T cells or NK cells), wherein: (a) the median GeneSetScore (Up TEM vs. Down TSCM) of the population of cells is about the same as or differs by no more than (for example, increased by no more than) about 25, 50, 75, 100, or 125% from the median GeneSetScore (Up TEM vs. Down TSCM) of the same population of cells prior to being engineered to express the CAR; (b) the median GeneSetScore (Up Treg vs. Down Teff) of the population of cells is about the same as or differs by no more than (for example, increased by no more than) about 25, 50, 100, 150, or 200% from the median GeneSetScore (Up Treg vs. Down Teff) of the population of cells prior to being engineered to express the CAR; (c) the median GeneSetScore (Down stemness) of the population of cells is about the same as or differs by no more than (for example, increased by no more than) about 25, 50, 100, 150, 200, or 250% from the median GeneSetScore (Down stemness) of the population of cells prior to being engineered to express the CAR; (d) the median GeneSetScore (Up hypoxia) of the population of cells is about the same as or differs by no more than (for example, increased by no more than) about 125, 150, 175, or 200% from the median GeneSetScore (Up hypoxia) of the population of cells prior to being engineered to express the CAR; or (e) the median GeneSetScore (Up autophagy) of the population of cells is about the same as or differs by no more than (for example, increased by no more than) about 180, 190, 200, or 210% from the median GeneSetScore (Up autophagy) of the population of cells prior to being engineered to express the CAR.

In some embodiments, this invention features a method of increasing an immune response in a subject, comprising administering a population of CAR-expressing cells dis-

closed herein or a pharmaceutical composition disclosed herein to the subject, thereby increasing an immune response in the subject.

In some embodiments, disclosed herein is a method of treating a cancer in a subject, comprising administering a population of CAR-expressing cells disclosed herein or a pharmaceutical composition disclosed herein to the subject, thereby treating the cancer in the subject. In some embodiments, the cancer is a solid cancer, for example, chosen from: one or more of mesothelioma, malignant pleural mesothelioma, non-small cell lung cancer, small cell lung cancer, squamous cell lung cancer, large cell lung cancer, pancreatic cancer, pancreatic ductal adenocarcinoma, esophageal adenocarcinoma, breast cancer, glioblastoma, ovarian cancer, colorectal cancer, prostate cancer, cervical cancer, skin cancer, melanoma, renal cancer, liver cancer, brain cancer, thymoma, sarcoma, carcinoma, uterine cancer, kidney cancer, gastrointestinal cancer, urothelial cancer, pharynx cancer, head and neck cancer, rectal cancer, esophagus cancer, or bladder cancer, or a metastasis thereof. In some embodiments, the cancer is a liquid cancer, for example, chosen from: chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), multiple myeloma, acute lymphoid leukemia (ALL), Hodgkin lymphoma, B-cell acute lymphoid leukemia (BALL), T-cell acute lymphoid leukemia (TALL), small lymphocytic leukemia (SLL), B cell prolymphocytic leukemia, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, diffuse large B cell lymphoma (DLBCL), DLBCL associated with chronic inflammation, chronic myeloid leukemia, myeloproliferative neoplasms, follicular lymphoma, pediatric follicular lymphoma, hairy cell leukemia, small cell- or a large cell-follicular lymphoma, malignant lymphoproliferative conditions, MALT lymphoma (extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue), Marginal zone lymphoma, myelodysplasia, myelodysplastic syndrome, non-Hodgkin lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenstrom macroglobulinemia, splenic marginal zone lymphoma, splenic lymphoma/leukemia, splenic diffuse red pulp small B-cell lymphoma, hairy cell leukemia-variant, lymphoplasmacytic lymphoma, a heavy chain disease, plasma cell myeloma, solitary plasmacytoma of bone, extraosseous plasmacytoma, nodal marginal zone lymphoma, pediatric nodal marginal zone lymphoma, primary cutaneous follicle center lymphoma, lymphomatoid granulomatosis, primary mediastinal (thymic) large B-cell lymphoma, intravascular large B-cell lymphoma, ALK+ large B-cell lymphoma, large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease, primary effusion lymphoma, B-cell lymphoma, acute myeloid leukemia (AML), or unclassifiable lymphoma.

In some embodiments, the method further comprises administering a second therapeutic agent to the subject. In some embodiments, the second therapeutic agent is an anti-cancer therapeutic agent, for example, a chemotherapy, a radiation therapy, or an immune-regulatory therapy. In some embodiments, the second therapeutic agent is IL-15 (for example, hetIL-15 (IL15/sIL-15Ra)).

In some embodiments, provided herein is an isolated cell or a population of cells made by a method as described herein comprising one or more cells comprising:

(a) a first nucleic acid molecule encoding a first CAR that comprises an anti-BCMA binding domain, a first transmembrane domain, and a first intracellular signaling domain, wherein the anti-BCMA binding domain comprises a heavy chain variable region (VH) comprising

- a heavy chain complementary determining region 1 (HC CDR1), a heavy chain complementary determining region 2 (HC CDR2), and a heavy chain complementary determining region 3 (HC CDR3), and a light chain variable region (VL) comprising a light chain complementary determining region 1 (LC CDR1), a light chain complementary determining region 2 (LC CDR2), and a light chain complementary determining region 3 (LC CDR3), wherein the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequences of SEQ ID NOS: 86, 87, 88, 95, 96, and 97, respectively; and
- (b) a second nucleic acid molecule encoding a second CAR that comprises an anti-CD19 binding domain, a second transmembrane domain, and a second intracellular signaling domain, wherein the anti-CD19 binding domain comprises a VH comprising a HC CDR1, a HC CDR2, and a HC CDR3, and a VL comprising a LC CDR1, a LC CDR2, and a LC CDR3, wherein the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequences of SEQ ID NOS: 295, 304, and 297-300, respectively.

In some embodiments, provided herein is an isolated cell comprising:

- (a) a first nucleic acid molecule encoding a first CAR that comprises an anti-BCMA binding domain, a first transmembrane domain, and a first intracellular signaling domain, wherein the anti-BCMA binding domain comprises a heavy chain variable region (VH) comprising a heavy chain complementary determining region 1 (HC CDR1), a heavy chain complementary determining region 2 (HC CDR2), and a heavy chain complementary determining region 3 (HC CDR3), and a light chain variable region (VL) comprising a light chain complementary determining region 1 (LC CDR1), a light chain complementary determining region 2 (LC CDR2), and a light chain complementary determining region 3 (LC CDR3), wherein the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequences of SEQ ID NOS: 86, 87, 88, 95, 96, and 97, respectively; and
- (b) a second nucleic acid molecule encoding a second CAR that comprises an anti-CD19 binding domain, a second transmembrane domain, and a second intracellular signaling domain, wherein the anti-CD19 binding domain comprises a VH comprising a HC CDR1, a HC CDR2, and a HC CDR3, and a VL comprising a LC CDR1, a LC CDR2, and a LC CDR3, wherein the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequences of SEQ ID NOS: 295, 304, and 297-300, respectively.

In some embodiments, the VH and VL of the anti-BCMA binding domain comprise the amino acid sequences of SEQ ID NOS: 93 and 102, respectively. In some embodiments, the VH and VL of the anti-CD19 binding domain comprise the amino acid sequences of SEQ ID NOS: 250 and 251, respectively. In some embodiments, the VH and VL of the anti-BCMA binding domain comprise the amino acid sequences of SEQ ID NOS: 93 and 102, respectively, and the VH and VL of the anti-CD19 binding domain comprise the amino acid sequences of SEQ ID NOS: 250 and 251, respectively. In some embodiments, the anti-BCMA binding domain comprises the amino acid sequence of SEQ ID NO: 105. In some embodiments, the anti-CD19 binding domain comprises the amino acid sequence of SEQ ID NO: 293. In some embodiments, the anti-BCMA binding domain comprises the amino acid sequence of SEQ ID NO: 105 and the

anti-CD19 binding domain comprises the amino acid sequence of SEQ ID NO: 293. In some embodiments, the first CAR comprises the amino acid sequence of SEQ ID NO: 107. In some embodiments, the second CAR comprise the amino acid sequence of SEQ ID NO: 225. In some embodiments, the first CAR comprises the amino acid sequence of SEQ ID NO: 107; and the second CAR comprise the amino acid sequence of SEQ ID NO: 225. In some embodiments, the first CAR is encoded by the nucleic acid sequence of SEQ ID NO: 259, 258, or 416. In some embodiments, the second CAR is encoded by the nucleic acid sequence of SEQ ID NO: 417, 355, 356, or 354. In some embodiments, the first CAR is encoded by the nucleic acid sequence of SEQ ID NO: 259, 258, or 416, and the second CAR is encoded by the nucleic acid sequence of SEQ ID NO: 417, 355, 356, or 354.

In some embodiments, provided herein is a pharmaceutical composition comprising the cell or population of cells, as described herein.

In some embodiments, provided herein is method of providing anti-tumor immunity in a subject or treating a subject having a disease associated with expression of BCMA comprising administering to the subject an effective amount of the cell or population of cells or the pharmaceutical composition, as described herein.

In some embodiments, the disease associated with BCMA expression is a hematologic cancer or a solid cancer, e.g., a hematologic cancer or a solid cancer described herein.

In some embodiments, the disease is chosen from: acute 30 leukemia, B-cell acute lymphoid leukemia ("BALL"), T-cell acute lymphoid leukemia ("TALL"), acute lymphoid leukemia (ALL), chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL), B cell prolymphocytic leukemia, blastic plasmacytoid dendritic cell neoplasm, Burkitt's 35 lymphoma, diffuse large B cell lymphoma, follicular lymphoma, hairy cell leukemia, small cell- or large cell-follicular lymphoma, malignant lymphoproliferative conditions, MALT lymphoma, mantle cell lymphoma, Marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin's lymphoma, 40 plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenstrom macroglobulinemia, prostate cancer (e.g., castrate-resistant or therapy-resistant prostate cancer, or metastatic prostate cancer), pancreatic cancer, lung cancer, 45 a plasma cell proliferative disorder (e.g., asymptomatic myeloma (smoldering multiple myeloma or indolent myeloma), monoclonal gammopathy of undetermined significance (MGUS), Waldenstrom's macroglobulinemia, plasmacytoma (e.g., plasma cell dyscrasia, solitary myeloma, solitary plasmacytoma, extramedullary plasmacytoma, and multiple plasmacytoma), systemic amyloid light chain amyloidosis, or POEMS syndrome (also known as Crow-Fukase syndrome, Takatsuki disease, and PEP syndrome)), or a combination thereof.

In some embodiments, the disease is multiple myeloma.

Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references (for example, sequence database reference numbers) mentioned herein are incorporated by reference in their entirety. For example, all GenBank, UniGene, and Entrez sequences referred to herein, for example, in any Table herein, are incorporated by reference. When one gene or protein references a plurality of sequence accession numbers, all of the sequence variants are encompassed.

In addition, the materials, methods, and examples are illustrative only and not intended to be limiting. Headings, sub-headings or numbered or lettered elements, for example, (a), (b), (i) etc., are presented merely for ease of reading. The use of headings or numbered or lettered elements in this document does not require the steps or elements be performed in alphabetical order or that the steps or elements are necessarily discrete from one another. Other features, objects, and advantages of the invention will be apparent from the description and drawings, and from the claims.

## BRIEF DESCRIPTION OF THE FIGURES

FIGS. 1A-1H: Jurkat NFAT Luciferase (JNL) reporter assay using an automated system was used to test the function of BCMA CARs. CAR clones were evaluated in the JNL reporter assay for antigen-dependent activity. JNL cells containing the indicated CAR clones or untransduced JNL cells (UTD) were co-cultured with media alone (FIGS. 1G and 1H) or with target cells lines (KMS11 as a BCMA-positive cell line (FIGS. 1A and 1C) and NALM6 as a BCMA-negative cell line (FIGS. 1E and 1F)) at different ratios and luciferase activity was measured as luminescence intensity. Clones were considered active when the luminescence intensity exceeded 2-fold the level of UTD cells in the presence of antigen-expressing cells. Luminescence readout is a direct measurement of CAR stimulation. FIGS. 1B and 1D are graphs showing expression level of BCMA CARs on JNL cells were detected by flow cytometry using a human recombinant (r)BCMA\_Fc-AF647. 1x or 2x platform indicated 40,000 of H293 cells or 80,000 of H293 cells seeded for viral production.

FIG. 2: Expression level of BCMA CARs on primary human T cells. Cells were stained with a human rBCMA\_Fc-AF647 reagent and assayed by flow cytometry. The percentage of CAR+ cells and MFI are shown in the graph for day 5 and day 9 of cell culture. Data is summarized in Table 27, which includes the viral titer achieved for the respective CARs.

FIGS. 3A-3C: The ability of T cells expressing the indicated CARs to mediate cell lysis and cytokine production were evaluated against the KMS11 target cell line expressing firefly luciferase (KMS11-luc). FIG. 3A: CART cells were co-cultured with KMS11-luc target cells at the indicated E:T ratios. % cell killing was determined by the difference in luciferase signal between target cells without effector T cells (control) and with effector T cells (experimental), expressed as a percent of the control. UTD represents untransduced T cells. FIG. 3B: Background killing was observed for the BCMA-negative line NALM6. FIG. 3C: IFN $\gamma$  was measured by MSD in the supernatants collected at 24 h from these co-culture systems with a E:T ratio of 2.5. All data is expressed as the average+/-standard deviation.

FIGS. 4A-4C: CAR expression in T cells transduced with a MOI=5 (viral titer defined by the first CAR expressed in SupT1 cells). FIG. 4A is a table summarizing % CAR19, % BCMA CAR, % Double Positive, % CAR19-only, and % BCMA-CAR-only of different constructs. FIG. 4B is a set of flow cytometry plots showing the staining of cells for surface BCMA CAR expression (x-axis) and surface CD19 CAR expression (y-axis). FIG. 4C is a pair of bar graphs showing BCMA CAR MFI (upper panel) and CD19 CAR MFI (lower panel).

FIGS. 5A-5C: In vitro killing assay using Day 8 CART cells. FIGS. 5A-5C are a set of graphs showing % Killing

against BCMA-positive KMS11 cells, CD19-positive Nalm6 cells, or BCMA/CD19-negative cells, respectively, at the indicated E:T ratios.

FIGS. 6A-6D: In vitro cytokine production using Day 8 CART cells. FIGS. 6A-6D are a set of bar graphs showing IFN gamma production of CART cells when co-cultured with BCMA-positive KMS11 cells or CD19-positive Nalm6 cells.

FIGS. 7A-7C: Individual CAR expression of cells manufactured using the ARM process. FIGS. 7A-7B are histograms showing the expression pattern of both anti-BCMA and anti-CD19 CARs at 24h or 72 h post-transduction of human primary T cells manufactured using the ARM process. The studies used a MOI of 1 based on the SupT1 titer determined by expression of the upstream CAR. In each of FIGS. 7A and 7B, the left part is a panel of histograms showing staining using rBCMA-Fc, and the right part is a panel of histograms showing staining using anti-idiotype antibody that binds to CD19 CAR. Constructs #244 ("c244") and #245 ("c245") are mono anti-CD19 CAR and mono anti-BCMA CAR, respectively. FIG. 7C is a panel of flow cytometry plots showing the anti-BCMA and anti-CD19 CAR expression pattern at 72 h post-transduction of human primary T cells using a MOI of 1 based on the upstream CAR titer.

FIGS. 8A-8C: In vivo anti-tumor activity of construct #236 ("c236") and construct #238 ("c238") using three mouse models: a disseminated KMS-11 (BCMA+CD19-) multiple myeloma model, expressing a luciferase reporter gene (KMS11-Luc) (FIG. 8A), a Nalm6-Luc (CD19+ BCMA-) xenograft mouse model (FIG. 8B) and a mixed model of 95% KMS-luc with 5% NALM6-Luc cells (FIG. 8C). The tumor burden is expressed as total body luminescence (p/s), depicted as mean tumor burden+SEM. On day 35 7 or 8 post tumor inoculation, mice were treated with c236 and c238 at designated doses of BCMA CAR+ or CD19 CAR+ T cell (approximate number of viable CAR+ T cells), as shown in Table 30. Vehicle (PBS) and non-transduced T cells (UTD) served as negative controls. Mono anti-BCMA CAR PI61 and mono anti-CD19 CAR CTL119 were also used as controls.

FIGS. 9A-9C: Body weight loss induced by graft-versus-host response. All mice were individually monitored for body weight loss, as a read-out for X-GvHD by measuring body weight over time. Body weight (BWT) is plotted as % change from baseline.

FIGS. 10A-10C: In vivo expansion of peripheral blood CD3+ T cells was analyzed by flow cytometry up to 4 weeks after infusion.

FIGS. 11A-11C: In vivo expansion of CAR+ T cells (BCMA CAR+ percentage) was analyzed by flow cytometry up to 4 weeks after infusion.

FIGS. 12A-12C: In vivo expansion of CAR+ T cells (double CAR+ counts) was analyzed by flow cytometry up to 4 weeks after infusion.

FIGS. 13A-13C: In vivo plasma IFN- $\gamma$  kinetics. Plasma IFN- $\gamma$  levels from all three mouse models treated with c236 and c238, as well as monoCAR controls, at respective CAR-T doses are plotted in the graphs. Mice were bled and plasma cytokine measured by MSD assay.

FIGS. 14A and 14B: In vivo efficacy and cellular expansion of cells generated using 236 and c238 in a multiple myeloma xenograft mouse model. FIG. 14A: NSG mice were injected with multiple myeloma cell line KMS11, which expressed a luciferase reporter gene. The tumor burden is expressed as total body luminescence (p/s), depicted as mean tumor burden+SEM. On day 8 post tumor

inoculation, mice were treated with c236 and c238 at 9e4 BCMA-CD19 double CAR+ T cell dose (approximate number of viable CAR+ T cells). Vehicle (PBS) and non-transduced T cells (UTD) served as negative controls. FIG. 14B: The expansion of peripheral blood CAR+ T cells was analyzed by flow cytometry up to 4 weeks after infusion. Double anti-BCMA and CD19 CAR+ T cell expansion was observed in c236 and c238 CAR-T Rx groups.

FIGS. 15A and 15B: CAR expression of cells manufactured using the ARM process. Flow cytometry plots showing the expression of double positive anti-BCMA and anti-CD19 CARs at 96h (FIG. 15A) and 7 days (FIG. 15B) post viral addition to human primary T cells manufactured using the ARM process. The studies used a MOI of 2 based on the SupT1 titer determined by expression of double CAR (positive for PI61 or R1G5 clones and CTL119) detected by anti-idiotype antibody that binds to CD19CAR and recombinant BCMA\_Fc (AF647) that binds to PI61 or R1G5. Mono anti-BCMA CARTs PI61 and R1G5, and mono anti-CD19 CART CTL119 served as controls.

FIG. 16: CAR Expression at day 7 with TM process using MOI of 5. Flow cytometry plots showing the expression of double positive anti-BCMA and anti-CD19 CARs on day 7 post viral addition to human primary T cells manufactured using the TM process. The studies used a MOI of 5 based on the SupT1 titer determined by expression of double CAR (positive for PI61 or R1G5 clones and CTL119) detected by anti-idiotype antibody that binds to CD19CAR and recombinant BCMA\_Fc (AF647) that binds to PI61 or R1G5.

FIGS. 17A and 17B: In vitro specific killing of BCMA- or CD19-expressing tumor cells by T cells engineered with anti-BCMACAR and CD19CAR diabody constructs. The ability of T cells expressing PI61/CTL119 clones to mediate cell lysis was evaluated against the KMS11-Luc or NALM6-Luc target cell line. CART cells were co-cultured with BCMA+ KMS-11-luc or BCMA-NALM6-Luc target cells at the indicated E:T ratios for 20h, and % cell killing, determined by the difference in luciferase signal between target cells without effector T cells (control) and with effector T cells (experimental) expressed as a percent of the control, was measured as a surrogate for target cell lysis. UTD represents untransduced T cells. Mono PI61 or CTL119 served as controls.

FIGS. 18A and 18B: Cytokine production of T cells engineered with anti-BCMACAR and CD19CAR diabody constructs in response to BCMA- or CD19-expressing tumor cells. IFN- $\gamma$  (FIG. 18A) and IL-2 (FIG. 18B) were measured by MSD in the supernatants from the killing assay co-culture at a ratio of 1.25:1.

FIG. 19: Percentages of the double CAR positive population, BCMA CAR positive population, and CD19 CAR positive population on Day 4.

FIG. 20: Flow cytometry plots showing staining of cells with rBCMA-Fc and an anti-idiotype antibody that binds to CD19 CAR.

FIG. 21: Percentages of total CAR positive populations on Day 4 and Day 7 under the indicated conditions.

FIG. 22: Cell counts (left panel) and percentage of live cells (right panel) on Days 0, 1, 3, and 7 under the indicated conditions.

FIGS. 23A, 23B, and 23C: Single cell RNA-seq data for input cells (FIG. 23A), Day 1 cells (FIG. 23B), and Day 9 cells (FIG. 23C). The “nGene” graphs show the number of expressed genes per cell. The “nUMI” graphs show the number of unique molecular identifiers (UMIs) per cell.

FIGS. 24A, 24B, 24C, and 24D: T-Distributed Stochastic Neighbor Embedding (TSNE) plots comparing input cells

(FIG. 24A), Day 1 cells (FIG. 24B), and Day 9 cells (FIG. 24C) for a proliferation signature, which was determined based on expression of genes CCNB1, CCND1, CCNE1, PLK1, and MKI67. Each dot represents a cell in that sample. Cells shown as light grey do not express the proliferation genes whereas dark shaded cells express one or more of the proliferation genes. FIG. 24D is a violin plot showing the distribution of gene set scores for a gene set comprised of genes that characterize a resting vs. activated T cell state for Day 1 cells, Day 9 cells, and input cells. In FIG. 24D, a higher gene set score (Up resting vs. Down activated) indicates an increasing resting T cell phenotype, whereas a lower gene set score (Up resting vs. Down activated) indicates an increasing activated T cell phenotype. Input cells were overall in more of a resting state compared to Day 9 and Day 1 cells. Day 1 cells show the greatest activation gene set score.

FIGS. 25A, 25B, 25C, 25D and 25E: Gene set analysis for input cells, Day 1 cells, and Day 9 cells. In FIG. 25A, a higher gene set score for the gene set “Up TEM vs. Down TSCM” indicates an increasing effector memory T cell (TEM) phenotype of the cells in that sample, whereas a lower gene set score indicates an increasing stem cell memory T cell (TSCM) phenotype. In FIG. 25B, a higher gene set score for the gene set “Up Treg vs. Down Teff” indicates an increasing regulatory T cell (Treg) phenotype, whereas a lower gene set score indicates an increasing effector T cell (Teff) phenotype. In FIG. 25C, a lower gene set score for the gene set “Down stemness” indicates an increasing stemness phenotype. In FIG. 25D, a higher gene set score for the gene set “Up hypoxia” indicates an increasing hypoxia phenotype. In FIG. 25E, a higher gene set score for the gene set “Up autophagy” indicates an increasing autophagy phenotype. Day 1 cells looked similar to the input cells in terms of memory, stem-like and differentiation signature. Day 9 cells, on the other hand, show a higher enrichment for metabolic stress.

FIGS. 26A, 26B, and 26C: Gene cluster analysis for input cells. FIGS. 26A-26C are violin plots showing the gene set scores from gene set analysis of the four clusters of the input cells. Each dot overlaying the violin plots in FIGS. 26A-26C represents a cell’s gene set score. In FIG. 26A, a higher gene set score of the gene set “Up Treg vs. Down Teff” indicates an increasing Treg cell phenotype, whereas a lower gene set score of the gene set “Up Treg vs. Down Teff” indicates an increasing Teff cell phenotype. In FIG. 26B, a higher gene set score of the gene set “Progressively up in memory differentiation” indicates an increasing late memory T cell phenotype, whereas a lower gene set score of the gene set “Progressively up in memory differentiation” indicates an increasing early memory T cell phenotype. In FIG. 26C, a higher gene set score of the gene set “Up TEM vs. Down TN” indicates an increasing effector memory T cell phenotype, whereas a lower gene set score of the gene set “Up TEM vs. Down TN” indicates an increasing naive T cell phenotype. The cells in Cluster 3 are shown to be in a later memory, further differentiated T cell state compared to the cells in Cluster 1 and Cluster 2 which are in an early memory, less differentiated T cell state. Cluster 0 appears to be in an intermediate T cell state. Taken together, this data shows that there is a considerable level of heterogeneity within input cells.

FIGS. 27A, 27B, and 27C: TCR sequencing and measuring clonotype diversity. Day 9 cells have flatter distribution of clonotype frequencies (higher diversity).

FIGS. 28A and 28B: Flow cytometry analyses for CAR expression on days 4 and 7 post-transduction. Flow cytometry

try analyses for CAR-T cells generated by co-transducing cells with BCMA and CD19CAR vectors at different combinations of MOIs with ARM process in a 24-well plate. FIG. 28A: Flow cytometry plots showed mono anti-BCMA CAR, mono anti-CD19 CAR and double+ CAR expression on days 4 and 7 post-transduction under four different MOI conditions in addition to controls (UTD and single vector). FIG. 28B: Quantification of subsets of CAR+ populations including total anti-BCMA CAR+ T cells, total anti-CD19 CAR+ T cells as well as total CAR+ T cells (sum of the two mono CAR+ T cells and double+ CAR T cells) in each condition as described in FIG. 28A. Data shown are one representative from three donor T cells with consistent results. CAR+ cell percentages are gated on live CD3+ T cell population.

FIG. 29: Flow cytometry analyses for CAR expression on day 4 post-transduction. Flow cytometry analyses of final products of dual targeting cocktail CART, mono BCMACART and mono CD19CART for CAR expression on day 4 post-transduction. A small aliquots of each product at 24h harvest were re-cultured for three days prior to flow cytometry staining.

FIGS. 30A, 30B, 30C, 30D, and 30E: In vivo efficacy of dual CART compared to mono BCMA CART and CD19 CART in xenograft models. NSG mice were injected with cell lines expressing the luciferase reporter gene (KMS-11, or Nalm-6, or a mix of both with 5% of Nalm-6-luc). The tumor burden is expressed as total body luminescence (p/s), depicted as mean tumor burden+SEM. On day 7 or 8 post tumor inoculation, mice were treated with dual targeting cocktail CART, BCMA CART, or CD19 CART at the respective doses (approximate number of viable CAR+ T cells). Vehicle (PBS) and non-transduced T cells (UTD) served as negative controls. N=5 mice for all groups. BCMACART and CD19CART served as respective controls using the highest dose level. All experiments were terminated on day 23 after CAR-T administration.

FIG. 31: FIG. 31 is a bar graph showing % mono CD19 CAR+ cells, % mono BCMA CAR+ cells, and % double BCMA/CD19 CAR+ cells on day 4 post transduction (day 3 past harvest).

FIG. 32: Characterization of T cell subsets. FIG. 32 is a graph showing % CD4+ T cells, CD8+ T cells, naïve T cells (Tn), central memory T cells (Tcm), effector memory T cells (Tem), and effector memory T cells re-expressing CD45RA (Temra), in the input material, post-enrichment material, and Day 1 Post-harvest material.

FIGS. 33A and 33B: Plasma IFN- $\gamma$  Kinetics of BCMA/CD19 dual CART cellular product, BCMA CART, and CD19 CART treated mice. Animals were treated with PBS, UTD, BCMA/CD19 dual CART cellular product, BCMA CART, or CD19 CART at respective CAR-T doses. Mice were bled and plasma cytokine measured by MSD assay.

## DETAILED DESCRIPTION

### Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention pertains.

The term “a” and “an” refers to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, “an element” means one element or more than one element.

The term “about” when referring to a measurable value such as an amount, a temporal duration, and the like, is meant to encompass variations of  $\pm 20\%$  or in some instances  $\pm 10\%$ , or in some instances  $\pm 5\%$ , or in some instances  $\pm 1\%$ , or in some instances  $\pm 0.1\%$  from the specified value, as such variations are appropriate to perform the disclosed methods.

The compositions and methods of the present invention encompass polypeptides and nucleic acids having the sequences specified, or sequences substantially identical or similar thereto, for example, sequences at least 85%, 90%, or 95% identical or higher to the sequence specified. In the context of an amino acid sequence, the term “substantially identical” is used herein to refer to a first amino acid sequence that contains a sufficient or minimum number of amino acid residues that are i) identical to, or ii) conservative substitutions of aligned amino acid residues in a second amino acid sequence such that the first and second amino acid sequences can have a common structural domain and/or common functional activity, for example, amino acid sequences that contain a common structural domain having at least about 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identity to a reference sequence, for example, a sequence provided herein.

In the context of a nucleotide sequence, the term “substantially identical” is used herein to refer to a first nucleic acid sequence that contains a sufficient or minimum number of nucleotides that are identical to aligned nucleotides in a second nucleic acid sequence such that the first and second nucleotide sequences encode a polypeptide having common functional activity, or encode a common structural polypeptide domain or a common functional polypeptide activity, for example, nucleotide sequences having at least about 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identity to a reference sequence, for example, a sequence provided herein.

The term “variant” refers to a polypeptide that has a substantially identical amino acid sequence to a reference amino acid sequence, or is encoded by a substantially identical nucleotide sequence. In some embodiments, the variant is a functional variant.

The term “functional variant” refers to a polypeptide that has a substantially identical amino acid sequence to a reference amino acid sequence, or is encoded by a substantially identical nucleotide sequence, and is capable of having one or more activities of the reference amino acid sequence.

The term cytokine (for example, IL-2, IL-7, IL-15, IL-21, or IL-6) includes full length, a fragment or a variant, for example, a functional variant, of a naturally-occurring cytokine (including fragments and functional variants thereof having at least 10%, 30%, 50%, or 80% of the activity, e.g., the immunomodulatory activity, of the naturally-occurring cytokine). In some embodiments, the cytokine has an amino acid sequence that is substantially identical (e.g., at least about 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identity) to a naturally-occurring cytokine, or is encoded by a nucleotide sequence that is substantially identical (e.g., at least about 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identity) to a naturally-occurring nucleotide sequence encoding a cytokine. In some embodiments, as understood in context, the cytokine further comprises a receptor domain, e.g., a cytokine receptor domain (e.g., an IL-15/IL-15R).

As used herein, the term “BCMA” refers to B-cell maturation antigen. BCMA (also known as TNFRSF17, BCM or CD269) is a member of the tumor necrosis receptor (TNFR) family and is predominantly expressed on terminally differentiated B cells, e.g., memory B cells, and plasma cells. Its

ligand is called B-cell activator of the TNF family (BAFF) and a proliferation inducing ligand (APRIL). BCMA is involved in mediating the survival of plasma cells for maintaining long-term humoral immunity. The gene for BCMA is encoded on chromosome 16 producing a primary mRNA transcript of 994 nucleotides in length (NCBI accession NM\_001192.2) that encodes a protein of 184 amino acids (NP\_001183.2). A second antisense transcript derived from the BCMA locus has been described, which may play a role in regulating BCMA expression. (Laabi Y. et al., Nucleic Acids Res., 1994, 22:1147-1154). Additional transcript variants have been described with unknown significance (Smirnova A S et al. Mol Immunol., 2008, 45(4): 1179-1183. A second isoform, also known as TV4, has been identified (Uniprot identifier Q02223-2). As used herein, "BCMA" includes proteins comprising mutations, e.g., point mutations, fragments, insertions, deletions and splice variants of full length wild-type BCMA.

The phrase "disease associated with expression of BCMA" includes, but is not limited to, a disease associated with a cell which expresses BCMA (e.g., wild-type or mutant BCMA) or condition associated with a cell which expresses BCMA (e.g., wild-type or mutant BCMA) including, e.g., proliferative diseases such as a cancer or malignancy or a precancerous condition such as a myelodysplasia, a myelodysplastic syndrome or a preleukemia; or a noncancer related indication associated with a cell which expresses BCMA (e.g., wild-type or mutant BCMA). For the avoidance of doubt, a disease associated with expression of BCMA may include a condition associated with a cell which does not presently express BCMA, e.g., because BCMA expression has been downregulated, e.g., due to treatment with a molecule targeting BCMA, e.g., a BCMA inhibitor described herein, but which at one time expressed BCMA. In one aspect, a cancer associated with expression of BCMA (e.g., wild-type or mutant BCMA) is a hematological cancer. In one aspect, the hematological cancer is a leukemia or a lymphoma. In one aspect, a cancer associated with expression of BCMA (e.g., wild-type or mutant BCMA) is a malignancy of differentiated plasma B cells. In one aspect, a cancer associated with expression of BCMA (e.g., wild-type or mutant BCMA) includes cancers and malignancies including, but not limited to, e.g., one or more acute leukemias including but not limited to, e.g., B-cell acute Lymphoid Leukemia ("BALL"), T-cell acute Lymphoid Leukemia ("TALL"), acute lymphoid leukemia (ALL); one or more chronic leukemias including but not limited to, e.g., chronic myelogenous leukemia (CML), Chronic Lymphoid Leukemia (CLL). Additional cancers or hematologic conditions associated with expression of BCMA (e.g., wild-type or mutant BCMA) comprise, but are not limited to, e.g., B cell prolymphocytic leukemia, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, diffuse large B cell lymphoma, Follicular lymphoma, Hairy cell leukemia, small cell- or a large cell-follicular lymphoma, malignant lymphoproliferative conditions, MALT lymphoma, mantle cell lymphoma, Marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin's lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenstrom macroglobulinemia, and "preleukemia" which are a diverse collection of hematological conditions united by ineffective production (or dysplasia) of myeloid blood cells, and the like. In some embodiments, the cancer is multiple myeloma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, or glioblastoma. In embodiments, a disease associated with expression of BCMA includes a plasma cell proliferative disorder,

e.g., asymptomatic myeloma (smoldering multiple myeloma or indolent myeloma), monoclonal gammopathy of undetermined significance (MGUS), Waldenstrom's macroglobulinemia, plasmacytomas (e.g., plasma cell dyscrasia, solitary myeloma, solitary plasmacytoma, extramedullary plasmacytoma, and multiple plasmacytoma), systemic amyloid light chain amyloidosis, and POEMS syndrome (also known as Crow-Fukase syndrome, Takatsuki disease, and PEP syndrome). Further diseases associated with expression of BCMA (e.g., wild-type or mutant BCMA) expression include, but not limited to, e.g., atypical and/or non-classical cancers, malignancies, precancerous conditions or proliferative diseases associated with expression of BCMA (e.g., wild-type or mutant BCMA), e.g., a cancer described herein, e.g., a prostate cancer (e.g., castrate-resistant or therapy-resistant prostate cancer, or metastatic prostate cancer), pancreatic cancer, or lung cancer.

Non-cancer related conditions that are associated with BCMA (e.g., wild-type or mutant BCMA) include viral infections; e.g., HIV, fungal infections, e.g., *C. neoformans*; autoimmune disease; e.g. rheumatoid arthritis, system lupus erythematosus (SLE or lupus), pemphigus vulgaris, and Sjogren's syndrome; inflammatory bowel disease, ulcerative colitis; transplant-related allo-specific immunity disorders related to mucosal immunity; and unwanted immune responses towards biologics (e.g., Factor VIII) where humoral immunity is important. In embodiments, a non-cancer related indication associated with expression of BCMA includes but is not limited to, e.g., autoimmune disease, (e.g., lupus), inflammatory disorders (allergy and asthma) and transplantation. In some embodiments, the tumor antigen-expressing cell expresses, or at any time expressed, mRNA encoding the tumor antigen. In an embodiment, the tumor antigen-expressing cell produces the tumor antigen protein (e.g., wild-type or mutant), and the tumor antigen protein may be present at normal levels or reduced levels. In an embodiment, the tumor antigen-expressing cell produced detectable levels of a tumor antigen protein at one point, and subsequently produced substantially no detectable tumor antigen protein.

The term "Chimeric Antigen Receptor" or alternatively a "CAR" or "CAR molecule" refers to a recombinant polypeptide construct comprising at least an extracellular antigen binding domain, a transmembrane domain and a cytoplasmic signaling domain (also referred to herein as "an intracellular signaling domain") comprising a functional signaling domain derived from a stimulatory molecule as defined below. In some embodiments, the domains in the CAR polypeptide construct are in the same polypeptide chain, for example, comprise a chimeric fusion protein. In some embodiments, the domains in the CAR polypeptide construct are not contiguous with each other, for example, are in different polypeptide chains, for example, as provided in an RCAR as described herein.

In some embodiments, the cytoplasmic signaling domain comprises a primary signaling domain (for example, a primary signaling domain of CD3-zeta). In some embodiments, the cytoplasmic signaling domain further comprises one or more functional signaling domains derived from at least one costimulatory molecule as defined below. In some embodiments, the costimulatory molecule is chosen from 41BB (i.e., CD137), CD27, ICOS, and/or CD28. In some embodiments, 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. In some embodiments, 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 costimulatory molecule and a functional signaling domain derived from a stimulatory molecule. In some embodiments, the CAR comprises 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 costimulatory molecule(s) and a functional signaling domain derived from a stimulatory molecule. In some embodiments, the CAR comprises 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 costimulatory molecule(s) and a functional signaling domain derived from a stimulatory molecule. In some embodiments the CAR comprises an optional leader sequence at the amino-terminus (N-terminus) of the CAR fusion protein. In some embodiments, the CAR further comprises a leader sequence at the N-terminus of the extracellular antigen recognition domain, wherein the leader sequence is optionally cleaved from the antigen recognition domain (for example, an scFv) during cellular processing and localization of the CAR to the cellular membrane.

A CAR that comprises an antigen binding domain (for example, an scFv, a single domain antibody, or TCR (for example, a TCR alpha binding domain or TCR beta binding domain)) that targets a specific tumor marker X, wherein X can be a tumor marker as described herein, is also referred to as XCAR. For example, a CAR that comprises an antigen binding domain that targets BCMA is referred to as BCMA CAR. The CAR can be expressed in any cell, for example, an immune effector cell as described herein (for example, a T cell or an NK cell).

The term “signaling domain” refers to the functional portion of a protein which acts by transmitting information within the cell to regulate cellular activity via defined signaling pathways by generating second messengers or functioning as effectors by responding to such messengers.

The term “antibody,” as used herein, refers to a protein, or polypeptide sequence derived from an immunoglobulin molecule, which specifically binds with an antigen. Antibodies can be polyclonal or monoclonal, multiple or single chain, or intact immunoglobulins, and may be derived from natural sources or from recombinant sources. Antibodies can be tetramers of immunoglobulin molecules.

The term “antibody fragment” refers to at least one portion of an intact antibody, or recombinant variants thereof, and refers to the antigen binding domain, for example, an antigenic determining variable region of an intact antibody, that is sufficient to confer recognition and specific binding of the antibody fragment to a target, such as an antigen. Examples of antibody fragments include, but are not limited to, Fab, Fab', F(ab')2, and Fv fragments, scFv antibody fragments, linear antibodies, single domain antibodies such as sdAb (either VL or VH), camelid VHH domains, and multi-specific molecules formed from antibody fragments such as a bivalent fragment comprising two or more, for example, two, Fab fragments linked by a disulfide bridge at the hinge region, or two or more, for example, two isolated CDR or other epitope binding fragments of an antibody linked. An antibody fragment can also be incorporated into single domain antibodies, maxibodies, minibodies, nanobodies, intrabodies, diabodies, triabodies, tetrabodies, v-NAR and bis-scFv (see, for example, Holl-

inger and Hudson, *Nature Biotechnology* 23:1126-1136, 2005). Antibody fragments can also be grafted into scaffolds based on polypeptides such as a fibronectin type III (Fn3) (see U.S. Pat. No. 6,703,199, which describes fibronectin polypeptide minibodies).

The term “scFv” refers to a fusion protein comprising at least one antibody fragment comprising a variable region of a light chain and at least one antibody fragment comprising a variable region of a heavy chain, wherein the light and heavy chain variable regions are contiguously linked via a short flexible polypeptide linker, and capable of being expressed as a single chain polypeptide, and wherein the scFv retains the specificity of the intact antibody from which it is derived. Unless specified, as used herein an scFv may have the VL and VH variable regions in either order, for example, with respect to the N-terminal and C-terminal ends of the polypeptide, the scFv may comprise VL-linker-VH or may comprise VH-linker-VL. In some embodiments, the scFv may comprise the structure of NH<sub>2</sub>-V<sub>L</sub>-linker-V<sub>H</sub>-COOH or NH<sub>2</sub>-V<sub>H</sub>-linker-V<sub>L</sub>-COOH.

The terms “complementarity determining region” or “CDR,” as used herein, refer to the sequences of amino acids within antibody variable regions which confer antigen specificity and binding affinity. For example, in general, there are three CDRs in each heavy chain variable region (for example, HCDR1, HCDR2, and HCDR3) and three CDRs in each light chain variable region (LCDR1, LCDR2, and LCDR3). The precise amino acid sequence boundaries of a given CDR can be determined using any of a number of well-known schemes, including those described by Kabat et al. (1991), “Sequences of Proteins of Immunological Interest,” 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD (“Kabat” numbering scheme), Al-Lazikani et al., (1997) JMB 273, 927-948 (“Chothia” numbering scheme), or a combination thereof. In a combined Kabat and Chothia numbering scheme, in some embodiments, the CDRs correspond to the amino acid residues that are part of a Kabat CDR, a Chothia CDR, or both.

The portion of the CAR composition of the invention comprising an antibody or antibody fragment thereof may exist in a variety of forms, for example, where the antigen binding domain is expressed as part of a polypeptide chain including, for example, a single domain antibody fragment (sdAb), a single chain antibody (scFv), or for example, a human or humanized antibody (Harlow et al., 1999, In: *Using Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, NY; Harlow et al., 1989, In: *Antibodies: A Laboratory Manual*, Cold Spring Harbor, New York; Houston et al., 1988, Proc. Natl. Acad. Sci. USA 85:5879-5883; Bird et al., 1988, Science 242:423-426). In some embodiments, the antigen binding domain of a CAR composition of the invention comprises an antibody fragment. In some embodiments, the CAR comprises an antibody fragment that comprises an scFv.

As used herein, the term “binding domain” or “antibody molecule” (also referred to herein as “anti-target binding domain”) refers to a protein, for example, an immunoglobulin chain or fragment thereof, comprising at least one immunoglobulin variable domain sequence. The term “binding domain” or “antibody molecule” encompasses antibodies and antibody fragments. In some embodiments, an antibody molecule is a multispecific antibody molecule, for example, it comprises a plurality of immunoglobulin variable domain sequences, wherein a first immunoglobulin variable domain sequence of the plurality has binding speci-

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ficity for a first epitope and a second immunoglobulin variable domain sequence of the plurality has binding specificity for a second epitope.

In some embodiments, a multispecific antibody molecule is a bispecific antibody molecule. A bispecific antibody has specificity for no more than two antigens. A bispecific antibody molecule is characterized by a first immunoglobulin variable domain sequence which has binding specificity for a first epitope and a second immunoglobulin variable domain sequence that has binding specificity for a second epitope.

The terms "bispecific antibody" and "bispecific antibodies" refer to molecules that combine the antigen binding sites of two antibodies within a single molecule. Thus, a bispecific antibody is able to bind two different antigens simultaneously or sequentially. Methods for making bispecific antibodies are well known in the art. Various formats for combining two antibodies are also known in the art.

Forms of bispecific antibodies of the invention include, but are not limited to, a diabody, a single-chain diabody, Fab dimerization (Fab-Fab), Fab-scFv, and a tandem antibody, as known to those of skill in the art.

The term "antibody heavy chain," refers to the larger of the two types of polypeptide chains present in antibody molecules in their naturally occurring conformations, and which normally determines the class to which the antibody belongs.

The term "antibody light chain," refers to the smaller of the two types of polypeptide chains present in antibody molecules in their naturally occurring conformations. Kappa (K) and lambda ( $\lambda$ ) light chains refer to the two major antibody light chain isotypes.

The term "recombinant antibody" refers to an antibody which is generated using recombinant DNA technology, such as, for example, an antibody expressed by a bacteriophage or yeast expression system. The term should also be construed to mean an antibody which has been generated by the synthesis of a DNA molecule encoding the antibody and which DNA molecule expresses an antibody protein, or an amino acid sequence specifying the antibody, wherein the DNA or amino acid sequence has been obtained using recombinant DNA or amino acid sequence technology which is available and well known in the art.

The term "antigen" or "Ag" refers to a molecule that provokes an immune response. This immune response may involve either antibody production, or the activation of specific immunologically-competent cells, or both. The skilled artisan will understand that any macromolecule, including virtually all proteins or peptides, can serve as an antigen. Furthermore, antigens can be derived from recombinant or genomic DNA. A skilled artisan will understand that any DNA, which comprises a nucleotide sequences or a partial nucleotide sequence encoding a protein that elicits an immune response therefore encodes an "antigen" as that term is used herein. Furthermore, one skilled in the art will understand that an antigen need not be encoded solely by a full length nucleotide sequence of a gene. It is readily apparent that the present invention includes, but is not limited to, the use of partial nucleotide sequences of more than one gene and that these nucleotide sequences are arranged in various combinations to encode polypeptides that elicit the desired immune response. Moreover, a skilled artisan will understand that an antigen need not be encoded by a "gene" at all. It is readily apparent that an antigen can be generated synthesized or can be derived from a biological sample, or might be macromolecule besides a polypeptide.

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Such a biological sample can include, but is not limited to a tissue sample, a tumor sample, a cell or a fluid with other biological components.

The terms "anti-tumor effect" and "anti-cancer effect" are used interchangeably and refer to a biological effect which can be manifested by various means, including but not limited to, for example, a decrease in tumor volume or cancer volume, a decrease in the number of tumor cells or cancer cells, a decrease in the number of metastases, an increase in life expectancy, a decrease in tumor cell proliferation or cancer cell proliferation, a decrease in tumor cell survival or cancer cell survival, or amelioration of various physiological symptoms associated with the cancerous condition. An "anti-tumor effect" or "anti-cancer effect" can also be manifested by the ability of the peptides, polynucleotides, cells and antibodies of the invention in prevention of the occurrence of tumor or cancer in the first place.

The term "autologous" refers to any material derived from the same individual to whom it is later to be re-introduced into the individual.

The term "allogeneic" refers to any material derived from a different animal of the same species as the individual to whom the material is introduced. Two or more individuals are said to be allogeneic to one another when the genes at one or more loci are not identical. In some embodiments, allogeneic material from individuals of the same species may be sufficiently unlike genetically to interact antigenically.

The term "xenogeneic" refers to a graft derived from an animal of a different species.

The term "apheresis" as used herein refers to the art-recognized extracorporeal process by which the blood of a donor or patient is removed from the donor or patient and passed through an apparatus that separates out selected particular constituent(s) and returns the remainder to the circulation of the donor or patient, for example, by retransfusion. Thus, in the context of "an apheresis sample" refers to a sample obtained using apheresis.

The term "cancer" refers to a disease characterized by the rapid and uncontrolled growth of aberrant cells. Cancer cells can spread locally or through the bloodstream and lymphatic system to other parts of the body. Examples of various cancers are described herein and include but are not limited to, breast cancer, prostate cancer, ovarian cancer, cervical cancer, skin cancer, pancreatic cancer, colorectal cancer, renal cancer, liver cancer, brain cancer, lymphoma, leukemia, lung cancer and the like. In some embodiments, cancers treated by the methods described herein include multiple myeloma, Hodgkin's lymphoma or non-Hodgkin's lymphoma.

The terms "tumor" and "cancer" are used interchangeably herein, for example, both terms encompass solid and liquid, for example, diffuse or circulating, tumors. As used herein, the term "cancer" or "tumor" includes premalignant, as well as malignant cancers and tumors.

"Derived from" as that term is used herein, indicates a relationship between a first and a second molecule. It generally refers to structural similarity between the first molecule and a second molecule and does not connote or include a process or source limitation on a first molecule that is derived from a second molecule. For example, in the case of an intracellular signaling domain that is derived from a CD3zeta molecule, the intracellular signaling domain retains sufficient CD3zeta structure such that it has the required function, namely, the ability to generate a signal under the appropriate conditions. It does not connote or include a limitation to a particular process of producing the intracel-

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lular signaling domain, for example, it does not mean that, to provide the intracellular signaling domain, one must start with a CD3zeta sequence and delete unwanted sequence, or impose mutations, to arrive at the intracellular signaling domain.

The term "conservative sequence modifications" refers to amino acid modifications that do not significantly affect or alter the binding characteristics of the antibody or antibody fragment containing the amino acid sequence. Such conservative modifications include amino acid substitutions, additions and deletions. Modifications can be introduced into an antibody or antibody fragment of the invention by standard techniques known in the art, such as site-directed mutagenesis and PCR-mediated mutagenesis. Conservative substitutions are ones in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (for example, lysine, arginine, histidine), acidic side chains (for example, aspartic acid, glutamic acid), uncharged polar side chains (for example, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine, tryptophan), nonpolar side chains (for example, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine), beta-branched side chains (for example, threonine, valine, isoleucine) and aromatic side chains (for example, tyrosine, phenylalanine, tryptophan, histidine). Thus, one or more amino acid residues within a CAR of the invention can be replaced with other amino acid residues from the same side chain family and the altered CAR can be tested using the functional assays described herein.

The term "stimulation" in the context of stimulation by a stimulatory and/or costimulatory molecule refers to a response, for example, a primary or secondary response, induced by binding of a stimulatory molecule (for example, a TCR/CD3 complex) and/or a costimulatory molecule (for example, CD28 or 4-1BB) with its cognate ligand thereby mediating a signal transduction event, such as, but not limited to, signal transduction via the TCR/CD3 complex. Stimulation can mediate altered expression of certain molecules and/or reorganization of cytoskeletal structures, and the like.

The term "stimulatory molecule," refers to a molecule expressed by a T cell that provides the primary cytoplasmic signaling sequence(s) that regulate primary activation of the TCR complex in a stimulatory way for at least some aspect of the T cell signaling pathway. In some embodiments, the ITAM-containing domain within the CAR recapitulates the signaling of the primary TCR independently of endogenous TCR complexes. In some embodiments, the primary signal is initiated by, for instance, binding of a TCR/CD3 complex with an MHC molecule loaded with peptide, and which leads to mediation of a T cell response, including, but not limited to, proliferation, activation, differentiation, and the like. A primary cytoplasmic signaling sequence (also referred to as a "primary signaling domain") that acts in a stimulatory manner may contain a signaling motif which is known as immunoreceptor tyrosine-based activation motif or ITAM. Examples of an ITAM containing primary cytoplasmic signaling sequence that is of particular use in the invention includes, but is not limited to, those derived from TCR zeta, FcR gamma, FcR beta, CD3 gamma, CD3 delta, CD3 epsilon, CD5, CD22, CD79a, CD79b, CD278 (also known as "ICOS"), FcεRI and CD66d, DAP10 and DAP12. In a specific CAR of the invention, the intracellular signaling domain in any one or more CARS of the invention comprises an intracellular signaling sequence, for example,

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primary signaling sequence of CD3-zeta. The term "antigen presenting cell" or "APC" refers to an immune system cell such as an accessory cell (for example, a B-cell, a dendritic cell, and the like) that displays a foreign antigen complexed with major histocompatibility complexes (MHC's) on its surface. T-cells may recognize these complexes using their T-cell receptors (TCRs). APCs process antigens and present them to T-cells.

An "intracellular signaling domain," as the term is used herein, refers to an intracellular portion of a molecule. In embodiments, the intracellular signal domain transduces the effector function signal and directs the cell to perform a specialized function. While the entire intracellular signaling domain can be employed, in many cases it is not necessary to use the entire chain. To the extent that a truncated portion of the intracellular signaling domain is used, such truncated portion may be used in place of the intact chain as long as it transduces the effector function signal. The term intracellular signaling domain is thus meant to include any truncated portion of the intracellular signaling domain sufficient to transduce the effector function signal.

The intracellular signaling domain generates a signal that promotes an immune effector function of the CAR containing cell, for example, a CART cell. Examples of immune effector function, for example, in a CART cell, include cytolytic activity and helper activity, including the secretion of cytokines.

In some embodiments, the intracellular signaling domain can comprise a primary intracellular signaling domain. Exemplary primary intracellular signaling domains include those derived from the molecules responsible for primary stimulation, or antigen dependent simulation. In some embodiments, the intracellular signaling domain can comprise a costimulatory intracellular domain. Exemplary costimulatory intracellular signaling domains include those derived from molecules responsible for costimulatory signals, or antigen independent stimulation. For example, in the case of a CART, a primary intracellular signaling domain can comprise a cytoplasmic sequence of a T cell receptor, and a costimulatory intracellular signaling domain can comprise cytoplasmic sequence from co-receptor or costimulatory molecule.

A primary intracellular signaling domain can comprise a signaling motif which is known as an immunoreceptor tyrosine-based activation motif or ITAM. Examples of ITAM containing primary cytoplasmic signaling sequences include, but are not limited to, those derived from CD3 zeta, FcR gamma, FcR beta, CD3 gamma, CD3 delta, CD3 epsilon, CD5, CD22, CD79a, CD79b, CD278 (also known as "ICOS"), FcεRI, CD66d, DAP10 and DAP12.

The term "zeta" or alternatively "zeta chain", "CD3-zeta" or "TCR-zeta" refers to CD247. Swiss-Prot accession number P20963 provides exemplary human CD3 zeta amino acid sequences. A "zeta stimulatory domain" or alternatively a "CD3-zeta stimulatory domain" or a "TCR-zeta stimulatory domain" refers to a stimulatory domain of CD3-zeta or a variant thereof (for example, a molecule having mutations, for example, point mutations, fragments, insertions, or deletions). In some embodiments, the cytoplasmic domain of zeta comprises residues 52 through 164 of GenBank Acc. No. BAG36664.1 or a variant thereof (for example, a molecule having mutations, for example, point mutations, fragments, insertions, or deletions). In some embodiments, the "zeta stimulatory domain" or a "CD3-zeta stimulatory domain" is the sequence provided as SEQ ID NO: 9 or 10,

or a variant thereof (for example, a molecule having mutations, for example, point mutations, fragments, insertions, or deletions).

The term “costimulatory molecule” refers to the cognate binding partner on a T cell that specifically binds with a costimulatory ligand, thereby mediating a costimulatory response by the T cell, such as, but not limited to, proliferation. Costimulatory molecules are cell surface molecules other than antigen receptors or their ligands that are required for an efficient immune response. Costimulatory molecules include, but are not limited to an MHC class I molecule, TNF receptor proteins, Immunoglobulin-like proteins, cytokine receptors, integrins, signaling lymphocytic activation molecules (SLAM proteins), activating NK cell receptors, BTLA, Toll ligand receptor, OX40, CD2, CD7, CD27, CD28, CD30, CD40, CDS, ICAM-1, LFA-1 (CD11a/CD18), 4-1BB (CD137), B7-H3, CDS, ICAM-1, ICOS (CD278), GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKP80 (KLRF1), NKP44, NKP30, NKP46, CD19, CD4, CD8alpha, CD8beta, IL2R beta, IL2R gamma, IL7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, NKG2C, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, CD28-OX40, CD28-4-1BB, and a ligand that specifically binds with CD83.

A costimulatory intracellular signaling domain refers to the intracellular portion of a costimulatory molecule.

The intracellular signaling domain can comprise the entire intracellular portion, or the entire native intracellular signaling domain, of the molecule from which it is derived, or a functional fragment thereof.

The term “4-1BB” refers to CD137 or Tumor necrosis factor receptor superfamily member 9. Swiss-Prot accession number P20963 provides exemplary human 4-1BB amino acid sequences. A “4-1BB costimulatory domain” refers to a costimulatory domain of 4-1BB, or a variant thereof (for example, a molecule having mutations, for example, point mutations, fragments, insertions, or deletions). In some embodiments, the “4-1BB costimulatory domain” is the sequence provided as SEQ ID NO: 7 or a variant thereof (for example, a molecule having mutations, for example, point mutations, fragments, insertions, or deletions).

“Immune effector cell,” as that term is used herein, refers to a cell that is involved in an immune response, for example, in the promotion of an immune effector response. Examples of immune effector cells include T cells, for example, alpha/beta T cells and gamma/delta T cells, B cells, natural killer (NK) cells, natural killer T (NKT) cells, mast cells, and myeloic-derived phagocytes.

“Immune effector function or immune effector response,” as that term is used herein, refers to function or response, for example, of an immune effector cell, that enhances or promotes an immune attack of a target cell. For example, an immune effector function or response refers a property of a T or NK cell that promotes killing or the inhibition of growth or proliferation, of a target cell. In the case of a T cell, primary stimulation and costimulation are examples of immune effector function or response.

The term “effector function” refers to a specialized function of a cell. Effector function of a T cell, for example, may be cytolytic activity or helper activity including the secretion of cytokines.

5 The term “encoding” refers to the inherent property of specific sequences of nucleotides in a polynucleotide, such as a gene, a cDNA, or an mRNA, to serve as templates for synthesis of other polymers and macromolecules in biological processes having either a defined sequence of nucleotides (for example, rRNA, tRNA and mRNA) or a defined sequence of amino acids and the biological properties resulting therefrom. Thus, a gene, cDNA, or RNA, encodes a protein if transcription and translation of mRNA corresponding to that gene produces the protein in a cell or other biological system. Both the coding strand, the nucleotide sequence of which is identical to the mRNA sequence and is usually provided in sequence listings, and the non-coding strand, used as the template for transcription of a gene or cDNA, can be referred to as encoding the protein or other product of that gene or cDNA.

10 Unless otherwise specified, a “nucleotide sequence encoding an amino acid sequence” includes all nucleotide sequences that are degenerate versions of each other and that encode the same amino acid sequence. The phrase nucleotide sequence that encodes a protein or a RNA may also include introns to the extent that the nucleotide sequence encoding the protein may in some version contain an intron(s).

15 The term “effective amount” or “therapeutically effective amount” are used interchangeably herein, and refer to an amount of a compound, formulation, material, or composition, as described herein effective to achieve a particular biological result.

20 The term “endogenous” refers to any material from or produced inside an organism, cell, tissue or system.

25 The term “exogenous” refers to any material introduced from or produced outside an organism, cell, tissue or system.

30 The term “expression” refers to the transcription and/or translation of a particular nucleotide sequence. In some embodiments, expression comprises translation of an mRNA introduced into a cell.

35 The term “transfer vector” refers to a composition of matter which comprises an isolated nucleic acid and which can be used to deliver the isolated nucleic acid to the interior of a cell. Numerous vectors are known in the art including, but not limited to, linear polynucleotides, polynucleotides associated with ionic or amphiphilic compounds, plasmids, and viruses. Thus, the term “transfer vector” includes an autonomously replicating plasmid or a virus. The term should also be construed to further include non-plasmid and non-viral compounds which facilitate transfer of nucleic acid into cells, such as, for example, a polylysine compound, liposome, and the like. Examples of viral transfer vectors include, but are not limited to, adenoviral vectors, adeno-associated virus vectors, retroviral vectors, lentiviral vectors, and the like.

40 The term “expression vector” refers to a vector comprising a recombinant polynucleotide comprising expression control sequences operatively linked to a nucleotide sequence to be expressed. An expression vector comprises sufficient cis-acting elements for expression; other elements for expression can be supplied by the host cell or in an in vitro expression system. Expression vectors include all those known in the art, including cosmids, plasmids (for example, naked or contained in liposomes) and viruses (for example,

lentiviruses, retroviruses, adenoviruses, and adeno-associated viruses) that incorporate the recombinant polynucleotide.

The term "lentivirus" refers to a genus of the Retroviridae family. Lentiviruses are unique among the retroviruses in being able to infect non-dividing cells; they can deliver a significant amount of genetic information into the DNA of the host cell, so they are one of the most efficient methods of a gene delivery vector. HIV, SIV, and FIV are all examples of lentiviruses.

The term "lentiviral vector" refers to a vector derived from at least a portion of a lentivirus genome, including especially a self-inactivating lentiviral vector as provided in Milone et al., Mol. Ther. 17(8): 1453-1464 (2009). Other examples of lentivirus vectors that may be used in the clinic, include but are not limited to, for example, the LENTIVECTOR® gene delivery technology from Oxford BioMedica, the LENTIMAX™ vector system from Lentigen and the like. Nonclinical types of lentiviral vectors are also available and would be known to one skilled in the art.

The term "homologous" or "identity" refers to the subunit sequence identity between two polymeric molecules, for example, between two nucleic acid molecules, such as, two DNA molecules or two RNA molecules, or between two polypeptide molecules. When a subunit position in both of the two molecules is occupied by the same monomeric subunit; for example, if a position in each of two DNA molecules is occupied by adenine, then they are homologous or identical at that position. The homology between two sequences is a direct function of the number of matching or homologous positions; for example, if half (for example, five positions in a polymer ten subunits in length) of the positions in two sequences are homologous, the two sequences are 50% homologous; if 90% of the positions (for example, 9 of 10), are matched or homologous, the two sequences are 90% homologous.

"Humanized" forms of non-human (for example, murine) antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', F(ab')2 or other antigen-binding subsequences of antibodies) which contain minimal sequence derived from non-human immunoglobulin. For the most part, humanized antibodies and antibody fragments thereof are human immunoglobulins (recipient antibody or antibody fragment) in which residues from a complementary-determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity, and capacity. In some instances, Fv framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, a humanized antibody/antibody fragment can comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. These modifications can further refine and optimize antibody or antibody fragment performance. In general, the humanized antibody or antibody fragment thereof will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or a significant portion of the FR regions are those of a human immunoglobulin sequence. The humanized antibody or antibody fragment can also comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. For further details, see Jones et al., Nature, 321: 522-525, 1986; Reichmann et al., Nature, 332: 323-329, 1988; Presta, Curr. Op. Struct. Biol., 2: 593-596, 1992.

"Fully human" refers to an immunoglobulin, such as an antibody or antibody fragment, where the whole molecule is of human origin or consists of an amino acid sequence identical to a human form of the antibody or immunoglobulin.

The term "isolated" means altered or removed from the natural state. For example, a nucleic acid or a peptide naturally present in a living animal is not "isolated," but the same nucleic acid or peptide partially or completely separated from the coexisting materials of its natural state is "isolated." An isolated nucleic acid or protein can exist in substantially purified form, or can exist in a non-native environment such as, for example, a host cell.

In the context of the present invention, the following abbreviations for the commonly occurring nucleic acid bases are used. "A" refers to adenosine, "C" refers to cytosine, "G" refers to guanosine, "T" refers to thymidine, and "U" refers to uridine.

The term "operably linked" or "transcriptional control" refers to functional linkage between a regulatory sequence and a heterologous nucleic acid sequence resulting in expression of the latter. For example, a first nucleic acid sequence is operably linked with a second nucleic acid sequence when the first nucleic acid sequence is placed in a functional relationship with the second nucleic acid sequence. For instance, a promoter is operably linked to a coding sequence if the promoter affects the transcription or expression of the coding sequence. Operably linked DNA sequences can be contiguous with each other and, for example, where necessary to join two protein coding regions, are in the same reading frame.

The term "parenteral" administration of an immunogenic composition includes, for example, subcutaneous (s.c.), intravenous (i.v.), intramuscular (i.m.), or intrasternal injection, intratumoral, or infusion techniques.

The term "nucleic acid," "nucleic acid molecule," "polynucleotide," or "polynucleotide molecule" refers to deoxyribonucleic acids (DNA) or ribonucleic acids (RNA) and polymers thereof in either single- or double-stranded form. Unless specifically limited, the term encompasses nucleic acids containing known analogues of natural nucleotides that have similar binding properties as the reference nucleic acid and are metabolized in a manner similar to naturally occurring nucleotides. In some embodiments, a "nucleic acid," "nucleic acid molecule," "polynucleotide," or "polynucleotide molecule" comprise a nucleotide/nucleoside derivative or analog. Unless otherwise indicated, a particular nucleic acid sequence also implicitly encompasses conservatively modified variants thereof (for example, degenerate codon substitutions, for example, conservative substitutions), alleles, orthologs, SNPs, and complementary sequences as well as the sequence explicitly indicated. Specifically, degenerate codon substitutions, for example, conservative substitutions may be achieved by generating sequences in which the third position of one or more selected (or all) codons is substituted with mixed-base and/or deoxyinosine residues (Batzer et al., Nucleic Acid Res. 19:5081 (1991); Ohtsuka et al., J. Biol. Chem. 260:2605-2608 (1985); and Rossolini et al., Mol. Cell. Probes 8:91-98 (1994)).

The terms "peptide," "polypeptide," and "protein" are used interchangeably, and refer to a compound comprised of amino acid residues covalently linked by peptide bonds. A protein or peptide must contain at least two amino acids, and no limitation is placed on the maximum number of amino acids that can comprise a protein's or peptide's sequence. Polypeptides include any peptide or protein comprising two

or more amino acids joined to each other by peptide bonds. As used herein, the term refers to both short chains, which also commonly are referred to in the art as peptides, oligopeptides and oligomers, for example, and to longer chains, which generally are referred to in the art as proteins, of which there are many types. "Polypeptides" include, for example, biologically active fragments, substantially homologous polypeptides, oligopeptides, homodimers, heterodimers, variants of polypeptides, modified polypeptides, derivatives, analogs, fusion proteins, among others. A polypeptide includes a natural peptide, a recombinant peptide, or a combination thereof.

The term "promoter" refers to a DNA sequence recognized by the synthetic machinery of the cell, or introduced synthetic machinery, required to initiate the specific transcription of a polynucleotide sequence.

The term "promoter/regulatory sequence" refers to a nucleic acid sequence which is required for expression of a gene product operably linked to the promoter/regulatory sequence. In some instances, this sequence may be the core promoter sequence and in other instances, this sequence may also include an enhancer sequence and other regulatory elements which are required for expression of the gene product. The promoter/regulatory sequence may, for example, be one which expresses the gene product in a tissue specific manner.

The term "constitutive" promoter refers to a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a cell under most or all physiological conditions of the cell.

The term "inducible" promoter refers to a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a cell substantially only when an inducer which corresponds to the promoter is present in the cell.

The term "tissue-specific" promoter refers to a nucleotide sequence which, when operably linked with a polynucleotide encodes or specified by a gene, causes the gene product to be produced in a cell substantially only if the cell is a cell of the tissue type corresponding to the promoter.

The terms "cancer associated antigen," "tumor antigen," "hyperproliferative disorder antigen," and "antigen associated with a hyperproliferative disorder" interchangeably refer to antigens that are common to specific hyperproliferative disorders. In some embodiments, these terms refer to a molecule (typically a protein, carbohydrate or lipid) that is expressed on the surface of a cancer cell, either entirely or as a fragment (for example, MHC/peptide), and which is useful for the preferential targeting of a pharmacological agent to the cancer cell. In some embodiments, a tumor antigen is a marker expressed by both normal cells and cancer cells, for example, a lineage marker, for example, CD19 on B cells. In some embodiments, a tumor antigen is a cell surface molecule that is overexpressed in a cancer cell in comparison to a normal cell, for instance, 1-fold over expression, 2-fold overexpression, 3-fold overexpression or more in comparison to a normal cell. In some embodiments, a tumor antigen is a cell surface molecule that is inappropriately synthesized in the cancer cell, for instance, a molecule that contains deletions, additions or mutations in comparison to the molecule expressed on a normal cell. In some embodiments, a tumor antigen will be expressed exclusively on the cell surface of a cancer cell, entirely or as a fragment (for example, MHC/peptide), and not synthesized or expressed on the surface of a normal cell. In some

embodiments, the hyperproliferative disorder antigens of the present invention are derived from, cancers including but not limited to primary or metastatic melanoma, thymoma, lymphoma, sarcoma, lung cancer, liver cancer, non-Hodgkin lymphoma, Hodgkin lymphoma, leukemias, uterine cancer, cervical cancer, bladder cancer, kidney cancer and adenocarcinomas such as breast cancer, prostate cancer (for example, castrate-resistant or therapy-resistant prostate cancer, or metastatic prostate cancer), ovarian cancer, pancreatic cancer, and the like, or a plasma cell proliferative disorder, for example, asymptomatic myeloma (smoldering multiple myeloma or indolent myeloma), monoclonal gammopathy of undetermined significance (MGUS), Waldenstrom's macroglobulinemia, plasmacytomas (for example, plasma cell dyscrasias, solitary myeloma, solitary plasmacytoma, extramedullary plasmacytoma, and multiple plasmacytoma), systemic amyloid light chain amyloidosis, and POEMS syndrome (also known as Crow-Fukase syndrome, Takatsuki disease, and PEP syndrome). In some embodiments, the CARs of the present invention include CARs comprising an antigen binding domain (for example, antibody or antibody fragment) that binds to a MHC presented peptide. Normally, peptides derived from endogenous proteins fill the pockets of Major histocompatibility complex (MHC) class I molecules and are recognized by T cell receptors (TCRs) on CD8+T lymphocytes. The MHC class I complexes are constitutively expressed by all nucleated cells. In cancer, virus-specific and/or tumor-specific peptide/MHC complexes represent a unique class of cell surface targets for immunotherapy. TCR-like antibodies targeting peptides derived from viral or tumor antigens in the context of human leukocyte antigen (HLA)-A1 or HLA-A2 have been described (see, for example, Sastry et al., J Virol. 2011 85(5):1935-1942; Sergeeva et al., Blood, 2011 117(16): 4262-4272; Verma et al., J Immunol 2010 184(4):2156-2165; Willemse et al., Gene Ther 2001 8(21):1601-1608; Dao et al., Sci Transl Med 2013 5(176):176ra33; Tashev et al., Cancer Gene Ther 2012 19(2):84-100). For example, TCR-like antibody can be identified from screening a library, such as a human scFv phage displayed library.

The term "tumor-supporting antigen" or "cancer-supporting antigen" interchangeably refer to a molecule (typically a protein, carbohydrate or lipid) that is expressed on the surface of a cell that is, itself, not cancerous, but supports the cancer cells, for example, by promoting their growth or survival for example, resistance to immune cells. Exemplary cells of this type include stromal cells and myeloid-derived suppressor cells (MDSCs). The tumor-supporting antigen itself need not play a role in supporting the tumor cells so long as the antigen is present on a cell that supports cancer cells.

The term "flexible polypeptide linker" or "linker" as used in the context of an scFv refers to a peptide linker that consists of amino acids such as glycine and/or serine residues used alone or in combination, to link variable heavy and variable light chain regions together. In some embodiments, the flexible polypeptide linker is a Gly/Ser linker and comprises the amino acid sequence (Gly-Gly-Gly-Ser)<sub>n</sub>, where n is a positive integer equal to or greater than 1 (SEQ ID NO: 41). For example, n=1, n=2, n=3, n=4, n=5 and n=6, n=7, n=8, n=9 and n=10. In some embodiments, the flexible polypeptide linkers include, but are not limited to, (Gly<sub>4</sub>Ser)<sub>4</sub> (SEQ ID NO: 27) or (Gly<sub>4</sub>Ser)<sub>3</sub> (SEQ ID NO: 28). In some embodiments, the linkers include multiple repeats of (Gly<sub>2</sub>Ser), (GlySer) or (Gly<sub>3</sub>Ser) (SEQ ID NO: 29). Also

included within the scope of the invention are linkers described in WO2012/138475, incorporated herein by reference.

As used herein, a 5' cap (also termed an RNA cap, an RNA 7-methylguanosine cap or an RNA m7G cap) is a modified guanine nucleotide that has been added to the "front" or 5' end of a eukaryotic messenger RNA shortly after the start of transcription. The 5' cap consists of a terminal group which is linked to the first transcribed nucleotide. Its presence is critical for recognition by the ribosome and protection from RNases. Cap addition is coupled to transcription, and occurs co-transcriptionally, such that each influences the other. Shortly after the start of transcription, the 5' end of the mRNA being synthesized is bound by a cap-synthesizing complex associated with RNA polymerase. This enzymatic complex catalyzes the chemical reactions that are required for mRNA capping. Synthesis proceeds as a multi-step biochemical reaction. The capping moiety can be modified to modulate functionality of mRNA such as its stability or efficiency of translation.

As used herein, "in vitro transcribed RNA" refers to RNA that has been synthesized in vitro. In some embodiments the RNA is mRNA. Generally, the in vitro transcribed RNA is generated from an in vitro transcription vector. The in vitro transcription vector comprises a template that is used to generate the in vitro transcribed RNA.

As used herein, a "poly(A)" is a series of adenosines attached by polyadenylation to the mRNA. In some embodiments of a construct for transient expression, the poly(A) is between 50 and 5000 (SEQ ID NO: 30). In some embodiments the poly(A) is greater than 64. In some embodiments the poly(A) is greater than 100. In some embodiments the poly(A) is greater than 300. In some embodiments the poly(A) is greater than 400. poly(A) sequences can be modified chemically or enzymatically to modulate mRNA functionality such as localization, stability or efficiency of translation.

As used herein, "polyadenylation" refers to the covalent linkage of a polyadenyl moiety, or its modified variant, to a messenger RNA molecule. In eukaryotic organisms, most messenger RNA (mRNA) molecules are polyadenylated at the 3' end. The 3' poly(A) tail is a long sequence of adenine nucleotides (often several hundred) added to the pre-mRNA through the action of an enzyme, polyadenylate polymerase. In higher eukaryotes, the poly(A) tail is added onto transcripts that contain a specific sequence, the polyadenylation signal. The poly(A) tail and the protein bound to it aid in protecting mRNA from degradation by exonucleases. Polyadenylation is also important for transcription termination, export of the mRNA from the nucleus, and translation. Polyadenylation occurs in the nucleus immediately after transcription of DNA into RNA, but additionally can also occur later in the cytoplasm. After transcription has been terminated, the mRNA chain is cleaved through the action of an endonuclease complex associated with RNA polymerase. The cleavage site is usually characterized by the presence of the base sequence AAUAAA near the cleavage site. After the mRNA has been cleaved, adenosine residues are added to the free 3' end at the cleavage site.

As used herein, "transient" refers to expression of a non-integrated transgene for a period of hours, days or weeks, wherein the period of time of expression is less than the period of time for expression of the gene if integrated into the genome or contained within a stable plasmid replicon in the host cell.

As used herein, the terms "treat", "treatment" and "treating" refer to the reduction or amelioration of the progres-

sion, severity and/or duration of a proliferative disorder, or the amelioration of one or more symptoms (preferably, one or more discernible symptoms) of a proliferative disorder resulting from the administration of one or more therapies (for example, one or more therapeutic agents such as a CAR of the invention). In specific embodiments, the terms "treat", "treatment" and "treating" refer to the amelioration of at least one measurable physical parameter of a proliferative disorder, such as growth of a tumor, not necessarily discernible by the patient. In other embodiments the terms "treat", "treatment" and "treating" refer to the inhibition of the progression of a proliferative disorder, either physically by, for example, stabilization of a discernible symptom, physiologically by, for example, stabilization of a physical parameter, or both. In other embodiments the terms "treat", "treatment" and "treating" refer to the reduction or stabilization of tumor size or cancerous cell count.

The term "signal transduction pathway" refers to the biochemical relationship between a variety of signal transduction molecules that play a role in the transmission of a signal from one portion of a cell to another portion of a cell. The phrase "cell surface receptor" includes molecules and complexes of molecules capable of receiving a signal and transmitting signal across the membrane of a cell.

The term "subject" is intended to include living organisms in which an immune response can be elicited (for example, mammals, for example, human).

The term, a "substantially purified" cell refers to a cell that is essentially free of other cell types. A substantially purified cell also refers to a cell which has been separated from other cell types with which it is normally associated in its naturally occurring state. In some instances, a population of substantially purified cells refers to a homogenous population of cells. In other instances, this term refers simply to cell that have been separated from the cells with which they are naturally associated in their natural state. In some embodiments, the cells are cultured *in vitro*. In some embodiments, the cells are not cultured *in vitro*.

The term "therapeutic" as used herein means a treatment. A therapeutic effect is obtained by reduction, suppression, remission, or eradication of a disease state.

The term "prophylaxis" as used herein means the prevention of or protective treatment for a disease or disease state.

The term "transfected" or "transformed" or "transduced" refers to a process by which exogenous nucleic acid is transferred or introduced into the host cell. A "transfected" or "transformed" or "transduced" cell is one which has been transfected, transformed or transduced with exogenous nucleic acid. The cell includes the primary subject cell and its progeny.

The term "specifically binds," refers to an antibody, or a ligand, which recognizes and binds with a cognate binding partner (for example, a stimulatory and/or costimulatory molecule present on a T cell) protein present in a sample, but which antibody or ligand does not substantially recognize or bind other molecules in the sample.

"Regulatable chimeric antigen receptor (RCAR)," as used herein, refers to a set of polypeptides, typically two in the simplest embodiments, which when in an immune effector cell, provides the cell with specificity for a target cell, typically a cancer cell, and with intracellular signal generation. In some embodiments, an RCAR comprises at least an extracellular antigen binding domain, a transmembrane domain and a cytoplasmic signaling domain (also referred to herein as "an intracellular signaling domain") comprising a functional signaling domain derived from a stimulatory molecule and/or costimulatory molecule as defined herein in

the context of a CAR molecule. In some embodiments, the set of polypeptides in the RCAR are not contiguous with each other, for example, are in different polypeptide chains. In some embodiments, the RCAR includes a dimerization switch that, upon the presence of a dimerization molecule, can couple the polypeptides to one another, for example, can couple an antigen binding domain to an intracellular signaling domain. In some embodiments, the RCAR is expressed in a cell (for example, an immune effector cell) as described herein, for example, an RCAR-expressing cell (also referred to herein as "RCARX cell"). In some embodiments the RCARX cell is a T cell and is referred to as a RCART cell. In some embodiments the RCARX cell is an NK cell, and is referred to as a RCARN cell. The RCAR can provide the RCAR-expressing cell with specificity for a target cell, typically a cancer cell, and with regulatable intracellular signal generation or proliferation, which can optimize an immune effector property of the RCAR-expressing cell. In embodiments, an RCAR cell relies at least in part, on an antigen binding domain to provide specificity to a target cell that comprises the antigen bound by the antigen binding domain.

"Membrane anchor" or "membrane tethering domain", as that term is used herein, refers to a polypeptide or moiety, for example, a myristoyl group, sufficient to anchor an extracellular or intracellular domain to the plasma membrane.

"Switch domain," as that term is used herein, for example, when referring to an RCAR, refers to an entity, typically a polypeptide-based entity, that, in the presence of a dimerization molecule, associates with another switch domain. The association results in a functional coupling of a first entity linked to, for example, fused to, a first switch domain, and a second entity linked to, for example, fused to, a second switch domain. A first and second switch domain are collectively referred to as a dimerization switch. In embodiments, the first and second switch domains are the same as one another, for example, they are polypeptides having the same primary amino acid sequence and are referred to collectively as a homodimerization switch. In embodiments, the first and second switch domains are different from one another, for example, they are polypeptides having different primary amino acid sequences, and are referred to collectively as a heterodimerization switch. In embodiments, the switch is intracellular. In embodiments, the switch is extracellular. In embodiments, the switch domain is a polypeptide-based entity, for example, FKBP or FRB-based, and the dimerization molecule is small molecule, for example, a rapalogue. In embodiments, the switch domain is a polypeptide-based entity, for example, an scFv that binds a myc peptide, and the dimerization molecule is a polypeptide, a fragment thereof, or a multimer of a polypeptide, for example, a myc ligand or multimers of a myc ligand that bind to one or more myc scFvs. In embodiments, the switch domain is a polypeptide-based entity, for example, myc receptor, and the dimerization molecule is an antibody or fragments thereof, for example, myc antibody.

"Dimerization molecule," as that term is used herein, for example, when referring to an RCAR, refers to a molecule that promotes the association of a first switch domain with a second switch domain. In embodiments, the dimerization molecule does not naturally occur in the subject or does not occur in concentrations that would result in significant dimerization. In embodiments, the dimerization molecule is a small molecule, for example, rapamycin or a rapalogue, for example, RAD001.

The term "low, immune enhancing, dose" when used in conjunction with an mTOR inhibitor, for example, an allos-

teric mTOR inhibitor, for example, RAD001 or rapamycin, or a catalytic mTOR inhibitor, refers to a dose of mTOR inhibitor that partially, but not fully, inhibits mTOR activity, for example, as measured by the inhibition of P70 S6 kinase activity. Methods for evaluating mTOR activity, for example, by inhibition of P70 S6 kinase, are discussed herein. The dose is insufficient to result in complete immune suppression but is sufficient to enhance the immune response. In some embodiments, the low, immune enhancing, dose of mTOR inhibitor results in a decrease in the number of PD-1 positive T cells and/or an increase in the number of PD-1 negative T cells, or an increase in the ratio of PD-1 negative T cells/PD-1 positive T cells. In some embodiments, the low, immune enhancing, dose of mTOR inhibitor results in an increase in the number of naive T cells. In some embodiments, the low, immune enhancing, dose of mTOR inhibitor results in one or more of the following: an increase in the expression of one or more of the following markers: CD62L<sup>high</sup> CD127<sup>high</sup> CD27+, and BCL2, for example, on memory T cells, for example, memory T cell precursors; a decrease in the expression of KLRG1, for example, on memory T cells, for example, memory T cell precursors; and an increase in the number of memory T cell precursors, for example, cells with any one or combination of the following characteristics: increased CD62L<sup>high</sup>, increased CD127<sup>high</sup>, increased CD27+, decreased KLRG1, and increased BCL2; wherein any of the changes described above occurs, for example, at least transiently, for example, as compared to a non-treated subject.

"Refractory" as used herein refers to a disease, for example, cancer, that does not respond to a treatment. In embodiments, a refractory cancer can be resistant to a treatment before or at the beginning of the treatment. In other embodiments, the refractory cancer can become resistant during a treatment. A refractory cancer is also called a resistant cancer.

"Relapsed" or "relapse" as used herein refers to the return or reappearance of a disease (for example, cancer) or the signs and symptoms of a disease such as cancer after a period of improvement or responsiveness, for example, after prior treatment of a therapy, for example, cancer therapy. The initial period of responsiveness may involve the level of cancer cells falling below a certain threshold, for example, below 20%, 1%, 10%, 5%, 4%, 3%, 2%, or 1%. The reappearance may involve the level of cancer cells rising above a certain threshold, for example, above 20%, 1%, 10%, 5%, 4%, 3%, 2%, or 1%. For example, for example, in the context of B-ALL, the reappearance may involve, for example, a reappearance of blasts in the blood, bone marrow (>5%), or any extramedullary site, after a complete response. A complete response, in this context, may involve <5% BM blast. More generally, in some embodiments, a response (for example, complete response or partial response) can involve the absence of detectable MRD (minimal residual disease). In some embodiments, the initial period of responsiveness lasts at least 1, 2, 3, 4, 5, or 6 days; at least 1, 2, 3, or 4 weeks; at least 1, 2, 3, 4, 6, 8, 10, or 12 months; or at least 1, 2, 3, 4, or 5 years.

Ranges: throughout this disclosure, various embodiments of the invention can be presented in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the invention. Accordingly, the description of a range should be considered

to have specifically disclosed all the possible subranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed subranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 2.7, 3, 4, 5, 5.3, and 6. As another example, a range such as 95-99% identity, includes something with 95%, 96%, 97%, 98%, or 99% identity, and includes subranges such as 96-99%, 96-98%, 96-97%, 97-99%, 97-98%, and 98-99% identity. This applies regardless of the breadth of the range.

A “gene editing system” as the term is used herein, refers to a system, for example, one or more molecules, that direct and effect an alteration, for example, a deletion, of one or more nucleic acids at or near a site of genomic DNA targeted by said system. Gene editing systems are known in the art and are described more fully below.

Administered "in combination", as used herein, means that two (or more) different treatments are delivered to the subject during the course of the subject's affliction with the disorder, for example, the two or more treatments are delivered after the subject has been diagnosed with the disorder and before the disorder has been cured or eliminated or treatment has ceased for other reasons. In some embodiments, the delivery of one treatment is still occurring when the delivery of the second begins, so that there is overlap in terms of administration. This is sometimes referred to herein as "simultaneous" or "concurrent delivery". In other embodiments, the delivery of one treatment ends before the delivery of the other treatment begins. In some embodiments of either case, the treatment is more effective because of combined administration. For example, the second treatment is more effective, for example, an equivalent effect is seen with less of the second treatment, or the second treatment reduces symptoms to a greater extent, than would be seen if the second treatment were administered in the absence of the first treatment, or the analogous situation is seen with the first treatment. In some embodiments, delivery is such that the reduction in a symptom, or other parameter related to the disorder is greater than what would be observed with one treatment delivered in the absence of the other. The effect of the two treatments can be partially additive, wholly additive, or greater than additive. The delivery can be such that an effect of the first treatment delivered is still detectable when the second is delivered.

The term "depletion" or "depleting", as used interchangeably herein, refers to the decrease or reduction of the level or amount of a cell, a protein, or macromolecule in a sample after a process, for example, a selection step, for example, a negative selection, is performed. The depletion can be a complete or partial depletion of the cell, protein, or macromolecule. In some embodiments, the depletion is at least a 1%, 2%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% decrease or reduction of the level or amount of a cell, a protein, or macromolecule, as compared to the level or amount of the cell, protein or macromolecule in the sample before the process was performed.

As used herein, a “naïve T cell” refers to a T cell that is antigen-inexperienced. In some embodiments, an antigen-inexperienced T cell has encountered its cognate antigen in the thymus but not in the periphery. In some embodiments, naïve T cells are precursors of memory cells. In some embodiments, naïve T cells express both CD45RA and CCR7, but do not express CD45RO. In some embodiments, naïve T cells may be characterized by expression of CD62L,

CD27, CCR7, CD45RA, CD28, and CD127, and the absence of CD95 or CD45RO isoform. In some embodiments, naïve T cells express CD62L, IL-7 receptor- $\alpha$ , IL-6 receptor, and CD132, but do not express CD25, CD44, 5 CD69, or CD45RO. In some embodiments, naïve T cells express CD45RA, CCR7, and CD62L and do not express CD95 or IL-2 receptor  $\beta$ . In some embodiments, surface expression levels of markers are assessed using flow cytometry.

10 The term “central memory T cells” refers to a subset of T  
cells that in humans are CD45RO positive and express  
CCR7. In some embodiments, central memory T cells  
express CD95. In some embodiments, central memory T  
cells express IL-2R, IL-7R and/or IL-15R. In some embodi-  
15 ments, central memory T cells express CD45RO, CD95,  
IL-2 receptor  $\beta$ , CCR7, and CD62L. In some embodiments,  
surface expression levels of markers are assessed using flow  
cytometry.

The term "stem memory T cells," "stem cell memory T cells," "stem cell-like memory T cells," "memory stem T cells," "T memory stem cells," "T stem cell memory cells" or "TSCM cells" refers to a subset of memory T cells with stem cell-like ability, for example, the ability to self-renew and/or the multipotent capacity to reconstitute memory and/or effector T cell subsets. In some embodiments, stem memory T cells express CD45RA, CD95, IL-2 receptor R, CCR7, and CD62L. In some embodiments, surface expression levels of markers are assessed using flow cytometry. In some embodiments, exemplary stem memory T cells are disclosed in Gattinoni et al., Nat Med. 2017 Jan. 6; 23(1): 18-27, herein incorporated by reference in its entirety.

For clarity purposes, unless otherwise noted, classifying a cell or a population of cells as "not expressing," or having an "absence of" or being "negative for" a particular marker 35 may not necessarily mean an absolute absence of the marker. The skilled artisan can readily compare the cell against a positive and/or a negative control, and/or set a predetermined threshold, and classify the cell or population of cells as not expressing or being negative for the marker when the 40 cell has an expression level below the predetermined threshold or a population of cells has an overall expression level below the predetermined threshold using conventional detection methods, e.g., using flow cytometry, for example, as described in the Examples herein.

As used herein, the term “GeneSetScore (Up TEM vs. Down TSCM)” of a cell refers to a score that reflects the degree at which the cell shows an effector memory T cell (TEM) phenotype vs. a stem cell memory T cell (TSCM) phenotype. A higher GeneSetScore (Up TEM vs. Down TSCM) indicates an increasing TEM phenotype, whereas a lower GeneSetScore (Up TEM vs. Down TSCM) indicates an increasing TSCM phenotype. In some embodiments, the GeneSetScore (Up TEM vs. Down TSCM) is determined by measuring the expression of one or more genes that are up-regulated in TEM cells and/or down-regulated in TSCM cells, for example, one or more genes selected from the group consisting of MXRA7, CLIC1, NAT13, TBC1D2B, GLCC11, DUSP10, APOBEC3D, CACNB3, ANXA2P2, TPRG1, EOMES, MATK, ARHGAP10, ADAM8, MAN1A1, SLFN12L, SH2D2A, EIF2C4, CD58, MYO1F, RAB27B, ERN1, NPC1, NBEAL2, APOBEC3G, SYTL2, SLC4A4, PIK3AP1, PTGDR, MAF, PLEKHA5, ADRB2, PLXND1, GNAO1, THBS1, PPP2R2B, CYTH3, KLRF1, FLJ16686, AUTS2, PTprm, GNLY, and GFPT2. In some embodiments, the GeneSetScore (Up TEM vs. Down TSCM) is determined for each cell using RNA-seq, for example, single-cell RNA-seq (scRNA-seq), for example, as

exemplified in Example 7 with respect to FIG. 25A. In some embodiments, the GeneSetScore (Up TEM vs. Down TSCM) is calculated by taking the mean log normalized gene expression value of all of the genes in the gene set.

As used herein, the term “GeneSetScore (Up Treg vs. Down Teff)” of a cell refers to a score that reflects the degree at which the cell shows a regulatory T cell (Treg) phenotype vs. an effector T cell (Teff) phenotype. A higher GeneSetScore (Up Treg vs. Down Teff) indicates an increasing Treg phenotype, whereas a lower GeneSetScore (Up Treg vs. Down Teff) indicates an increasing Teff phenotype. In some embodiments, the GeneSetScore (Up Treg vs. Down Teff) is determined by measuring the expression of one or more genes that are up-regulated in Treg cells and/or down-regulated in Teff cells, for example, one or more genes selected from the group consisting of C12orf75, SELPLG, SWAP70, RGS1, PRR11, SPATS2L, SPATS2L, TSHR, C14orf145, CASP8, SYT11, ACTN4, ANXA5, GLRX, HLA-DMB, PMCH, RAB11FIP1, IL32, FAM160B1, SHMT2, FRMD4B, CCR3, TNFRSF13B, NTNG2, CLDND1, BARD1, FCER1G, TYMS, ATP1B1, GJB6, FGL2, TK1, SLC2A8, CDKN2A, SKAP2, GPR55, CDCA7, S100A4, GDPD5, PMAIP1, ACOT9, CEP55, SGMS1, ADPRH, AKAP2, HDAC9, IKZF4, CARD17, VAV3, OBFC2A, ITGB1, CIITA, SETD7, HLA-DMA, CCR10, KIAA0101, SLC14A1, PTTG3P, DUSP10, FAM164A, PYHINI, MYO1F, SLC1A4, MYBL2, PTTG1, RRM2, TP53INP1, CCR5, ST8SIA6, TOX, BFSP2, ITPR1L1, NCAPH, HLA-DPB2, SYT4, NINJ2, FAM46C, CCR4, GBP5, C15orf53, LMCD1, MKI67, NUSAP1, PDE4A, E2F2, CD58, ARHGEF12, LOC100188949, FAS, HLA-DPB1, SELP, WEE1, HLA-DPA1, FCRL1, ICA1, CNTNAP1, OAS1, METTL7A, CCR6, HLA-DRB4, ANXA2P3, STAM, HLA-DQB2, LGALS1, ANXA2, P116, DUSP4, LAYN, ANXA2P2, PTPLA, ANXA2P1, ZNF365, LAIR2, LOC541471, RASGRP4, BCAS1, UTS2, MIAT, PRDM1, SEMA3G, FAM129A, HPGD, NCF4, LGALS3, CEACAM4, JAKMIP1, TIGIT, HLA-DRA, IKZF2, HLA-DRB1, FANK1, RTKN2, TRIB1, FCRL3, and FOXP3. In some embodiments, the GeneSetScore (Up Treg vs. Down Teff) is determined using RNA-seq, for example, single-cell RNA-seq (scRNA-seq), for example, as exemplified in Example 7 with respect to FIG. 25B. In some embodiments, the GeneSetScore (Up Treg vs. Down Teff) is calculated by taking the mean log normalized gene expression value of all of the genes in the gene set.

As used herein, the term “GeneSetScore (Down stemness)” of a cell refers to a score that reflects the degree at which the cell shows a stemness phenotype. A lower GeneSetScore (Down stemness) indicates an increasing stemness phenotype. In some embodiments, the GeneSetScore (Down stemness) is determined by measuring the expression of one or more genes that are upregulated in a differentiating stem cell vs downregulated in a hematopoietic stem cell, for example, one or more genes selected from the group consisting of ACE, BATF, CDK6, CHD2, ERCC2, HOXB4, MEOX1, SFRP1, SP7, SRF, TAL1, and XRCC5. In some embodiments, the GeneSetScore (Down stemness) is determined using RNA-seq, for example, single-cell RNA-seq (scRNA-seq), for example, as exemplified in Example 7 with respect to FIG. 25C. In some embodiments, the GeneSetScore (Down stemness) is calculated by taking the mean log normalized gene expression value of all of the genes in the gene set.

As used herein, the term “GeneSetScore (Up hypoxia)” of a cell refers to a score that reflects the degree at which the cell shows a hypoxia phenotype. A higher GeneSetScore

(Up hypoxia) indicates an increasing hypoxia phenotype. In some embodiments, the GeneSetScore (Up hypoxia) is determined by measuring the expression of one or more genes that are up-regulated in cells undergoing hypoxia, for example, one or more genes selected from the group consisting of ABCB1, ACAT1, ADM, ADORA2B, AK2, AK3, ALDH1A1, ALDH1A3, ALDOA, ALDOC, ANGPT2, ANGPTL4, ANXA1, ANXA2, ANXA5, ARHGAP5, ARSE, ART1, BACE2, BATF3, BCL2L1, BCL2L2, BHLHE40, BHLHE41, BIK, BIRC2, BNIP3, BNIP3L, BPI, BTG1, C11orf2, C7orf68, CA12, CA9, CALD1, CCNG2, CCT6A, CD99, CDK1, CDKN1A, CDKN1B, CITED2, CLK1, CNOT7, COL4A5, COL5A1, COL5A2, COL5A3, CP, CTSD, CXCR4, D4S234E, DDIT3, DDIT4, 1-Dec, DKC1, DR1, EDN1, EDN2, EFNA1, EGF, EGR1, EIF4A3, ELF3, ELL2, ENG, ENO1, ENO3, ENPEP, EPO, ERRFI1, ETS1, F3, FABP5, FGF3, FKBP4, FLT1, FN1, FOS, FTL, GAPDH, GBE1, GLRX, GPI, GPRC5A, HAPI, HBP1, HDAC1, HDAC9, HERC3, HERPUD1, HGF, HIF1A, HK1, HK2, HLA-DQB1, HMOX1, HMOX2, HSPA5, HSPD1, HSPH1, HYOU1, ICAM1, ID2, IFI27, IGF2, IGFBP1, IGFBP2, IGFBP3, IGFBP5, IL6, IL8, INSIG1, JRF6, ITGA5, JUN, KDR, KRT14, KRT18, KRT19, LDHA, LDHB, LEP, LGALS1, LONP1, LOX, LRP1, MAP4, MET, MIF, MMP13, MMP2, MMP7, MPI, MT1L, MTL3P, MUC1, MXII, NDRG1, NFIL3, NFKB1, NFKB2, NOS1, NOS2, NOS2P1, NOS2P2, NOS3, NR3C1, NR4A1, NTSE, ODC1, P4HA1, P4HA2, PAICS, PDGFB, PDK3, PFKFB1, PFKFB3, PFKFB4, PFKL, PGAM1, PGF, PGK1, PGK2, PGM1, PIM1, PIM2, PKM2, PLAU, PLAUR, PLIN2, PLOD2, PNN, PNP, POLM, PPARA, PPAT, PROK1, PSMA3, PSMD9, PTGS1, PTGS2, QSOX1, RBPJ, RELA, RIOK3, RNASEL, RPL36A, RRP9, SAT1, SERPINB2, SERPINE1, SGSM2, SIAH2, SIN3A, SIRPA, SLC16A1, SLC16A2, SLC20A1, SLC2A1, SLC2A3, SLC3A2, SLC6A10P, SLC6A16, SLC6A6, SLC6A8, SORL1, SPP1, SRSF6, SSSCA1, STC2, STRA13, SYT7, TBPL1, TCEAL1, TEK, TF, TFF3, TFRC, TGFA, TGFB1, TGFB3, TGFB1I, TGM2, TH, THBS1, THBS2, TIMM17A, TNFAIP3, TP53, TPBG, TPD52, TPI1, TXN, TXNIP, UMPS, VEGFA, VEGFB, VEGFC, VIM, VPS11, and XRCC6. In some embodiments, the GeneSetScore (Up hypoxia) is determined using RNA-seq, for example, single-cell RNA-seq (scRNA-seq), for example, as exemplified in Example 7 with respect to FIG. 25D. In some embodiments, the GeneSetScore (Up hypoxia) is calculated by taking the mean log normalized gene expression value of all of the genes in the gene set.

As used herein, the term “GeneSetScore (Up autophagy)” of a cell refers to a score that reflects the degree at which the cell shows an autophagy phenotype. A higher GeneSetScore (Up autophagy) indicates an increasing autophagy phenotype. In some embodiments, the GeneSetScore (Up autophagy) is determined by measuring the expression of one or more genes that are up-regulated in cells undergoing autophagy, for example, one or more genes selected from the group consisting of ABL1, ACBD5, ACIN1, ACTRT1, ADAMTS7, AKR1E2, ALKBH5, ALPK1, AMBRA1, ANXA5, ANXA7, ARSB, ASB2, ATG10, ATG12, ATG13, ATG14, ATG16L1, ATG16L2, ATG2A, ATG2B, ATG3, ATG4A, ATG4B, ATG4C, ATG4D, ATG5, ATG7, ATG9A, ATG9B, ATP13A2, ATP1B1, ATPAF1-AS1, ATPIF1, BECN1, BECN1P1, BLOC1S1, BMP2KL, BNIP1, BNIP3, BOC, C11orf2, C11orf41, C12orf44, C12orf5, C14orf133, C1orf210, C5, C6orf106, C7orf59, C7orf68, C8orf59, C9orf72, CA7, CALCB, CALCOCO2, CAPS, CCDC36, CD163L1, CD93, CDC37, CDKN2A, CHAF1B, CHMP2A,

CHMP2B, CHMP3, CHMP4A, CHMP4B, CHMP4C, CHMP6, CHST3, CISD2, CLDN7, CLEC16A, CLN3, CLVS1, COX8A, CPA3, CRNKL1, CSPG5, CTSA, CTSB, CTSD, CXCR7, DAP, DKKL1, DNAAF2, DPF3, DRAM1, DRAM2, DYNLL1, DYNLL2, DZANK1, EI24, EIF2S1, EPG5, EPM2A, FABP1, FAM125A, FAM131B, FAM134B, FAM13B, FAM176A, FAM176B, FAM48A, FANCC, FANCF, FANCL, FBXO7, FCGR3B, FGF14, FGF7, FGFBP1, FIS1, FNBP1L, FOXO1, FUNDC1, FUNDC2, FXR2, GABARAP, GABARAPL1, GABARAPL2, GABA-RAPL3, GABRA5, GDF5, GMIP, HAP1, HAPLN1, HBXIP, HCAR1, HDAC6, HGS, HIST1H3A, HIST1H3B, HIST1H3C, HIST1H3D, HIST1H3E, HIST1H3F, HIST1H3G, HIST1H3H, HIST1H3I, HIST1H3J, HK2, HMGB1, HPR, HSF2BP, HSP90AA1, HSPA8, IFI16, IPPK, IRGM, IST1, ITGB4, ITPKC, KCNK3, KCNQ1, KIAA0226, KIAA1324, KRCC1, KRT15, KRT73, LAMPI, LAMP2, LAMTOR1, LAMTOR2, LAMTOR3, LARPIB, LENG9, LGALS8, LIX1, LIX1L, LMCD1, LRRK2, LRSAM1, LSM4, MAP1A, MAP1LC3A, MAP1LC3B, MAP1LC3B2, MAP1LC3C, MAP1S, MAP2K1, MAP3K12, MARK2, MBD5, MDH1, MEX3C, MFN1, MFN2, MLST8, MRPS10, MRPS2, MSTN, MTERFD1, MTMR14, MTMR3, MTOR, MTSS1, MYH11, MYLK, MYOM1, NBR1, NDUFB9, NEFM, NHLRC1, NME2, NPC1, NR2C2, NRBF2, NTHL1, NUP93, OBSCN, OPTN, P2RX5, PACS2, PARK2, PARK7, PDK1, PDK4, PEX13, PEX3, PFKP, PGK2, PHF23, PHYHIP, PI4K2A, PIK3C3, PIK3CA, PIK3CB, PIK3R4, PINK1, PLEKHM1, PLOD2, PNPO, PPARGC1A, PPY, PRKAA1, PRKAA2, PRKAB1, PRKAB2, PRKAG1, PRKAG2, PRKAG3, PRKD2, PRKG1, PSEN1, PTPN22, RAB12, RAB1A, RAB1B, RAB23, RAB24, RAB33B, RAB39, RAB7A, RB1CC1, RBM18, REEP2, REP15, RFWD3, RGS19, RHEB, RIMS3, RNF185, RNF41, RPS27A, RPTOR, RRAGA, RRAGB, RRAGC, RRAGD, S100A8, S100A9, SCNA1, SERPINB10, SESN2, SFRP4, SH3GLB1, SIRT2, SLC1A3, SLC1A4, SLC22A3, SLC25A19, SLC35B3, SLC35C1, SLC37A4, SLC6A1, SLC01A2, SMURF1, SNAP29, SNA-PIN, SNF8, SNRNPB, SNRNPB2, SNRPD1, SNRPF, SNTG1, SNX14, SPATA18, SQSTM1, SRPX, STAM, STAM2, STAT2, STBD1, STK11, STK32A, STOM, STX12, STX17, SUPT3H, TBC1D17, TBC1D25, TBC1D5, TCIRG1, TEAD4, TECPR1, TECPR2, TFEB, TM9SF1, TMBIM6, TMEM203, TMEM208, TMEM39A, TMEM39B, TMEM59, TMEM74, TMEM93, TNK, TOLLIP, TOMM20, TOMM22, TOMM40, TOMM5, TOMM6, TOMM7, TOMM70A, TP53INP1, TP53INP2, TRAPPc8, TREM1, TRIM17, TRIMS, TSG101, TXLNA, UBA52, UBB, UBC, UBQLN1, UBQLN2, UBQLN4, ULK1, ULK2, ULK3, USP10, USP13, USP30, UVRAG, VAMP7, VAMP8, VDAC1, VMP1, VPS11, VPS16, VPS18, VPS25, VPS28, VPS33A, VPS33B, VPS36, VPS37A, VPS37B, VPS37C, VPS37D, VPS39, VPS41, VPS4A, VPS4B, VTA1, VTI1A, VTI1B, WDFY3, WDR45, WDR45L, WIP1, WIP12, XBP1, YIPF1, ZCCHC17, ZFYVE1, ZKSCAN3, ZNF189, ZNF593, and ZNF681. In some embodiments, the GeneSetScore (Up autophagy) is determined using RNA-seq, for example, single-cell RNA-seq (scRNA-seq), for example, as exemplified in Example 7 with respect to FIG. 25E. In some embodiments, the GeneSetScore (Up autophagy) is calculated by taking the mean log normalized gene expression value of all of the genes in the gene set.

As used herein, the term “GeneSetScore (Up resting vs. Down activated)” of a cell refers to a score that reflects the degree at which the cell shows a resting T cell phenotype vs.

an activated T cell phenotype. A higher GeneSetScore (Up resting vs. Down activated) indicates an increasing resting T cell phenotype, whereas a lower GeneSetScore (Up resting vs. Down activated) indicates an increasing activated T cell phenotype. In some embodiments, the GeneSetScore (Up resting vs. Down activated) is determined by measuring the expression of one or more genes that are up-regulated in resting T cells and/or down-regulated in activated T cells, for example, one or more genes selected from the group consisting of ABCA7, ABCF3, ACAP2, AMT, ANKH, ATF7IP2, ATG14, ATP1A1, ATXN7, ATXN7L3B, BCL7A, BEX4, BSDC1, BTG1, BTG2, BTN3A1, C11orf21, C19orf22, C21orf2, CAMK2G, CARS2, CCNL2, CD248, CD5, CD55, CEP164, CHKB, CLK1, CLK4, CTSL1, DBP, DCUN1D2, DENND1C, DGKD, DLG1, DUSP1, EAPP, ECE1, ECHDC2, ERBB2IP, FAM117A, FAM134B, FAM134C, FAM169A, FAM190B, FAU, FLJ10038, FOXJ2, FOXJ3, FOXL1, FOXO1, FXYD5, FYB, HLA-E, HSPA1L, HYAL2, ICAM2, IFIT5, IFITM1, IKBKB, IQSEC1, IRS4, KIAA0664L3, KIAA0748, KLF3, KLF9, KRT18, LEF1, LINC00342, LIPA, LIPT1, LLGL2, LMBR1L, LPAR2, LTBP2, LYPD3, LZTFL1, MANBA, MAP2K6, MAP3K1, MARCH8, MAU2, MGEA5, MMP8, MPO, MSL1, MSL3, MYH3, MYLIP, NAGPA, NDST2, NISCH, NKTR, NLRP1, NOSIP, NPIP, NUMA1, PAIP2B, PAPD7, PBXIP1, PCIF1, PI4KA, PLCL2, PLEKHA1, PLEKHF2, PNISR, PPFIBP2, PRKCA, PRKCZ, PRKD3, PRMT2, PTP4A3, PXN, RASA2, RASA3, RASGRP2, RBM38, REPIN1, RNF38, RNF44, ROR1, RPL30, RPL32, RPLP1, RPS20, RPS24, RPS27, RPS6, RPS9, RXRA, RYK, SCAND2, SEMA4C, SETD1B, SETD6, SETX, SF3B1, SH2B1, SLC2A4RG, SLC35E2B, SLC46A3, SMAGP, SMARCE1, SMPD1, SNPH, SP140L, SPATA6, SPG7, SREK1IP1, SRSF5, STAT5B, SVIL, SYF2, SYNJ2BP, TAF1C, TBC1D4, TCF20, TECTA, TES, TMEM127, TMEM159, TMEM30B, TMEM66, TMEM8B, TP53TG1, TPCN1, TRIM22, TRIM44, TSC1, TSC22D1, TSC22D3, TSPYL2, TTC9, TTN, UBE2G2, USP33, USP34, VAMP1, VILL, VIPR1, VPS13C, ZBED5, ZBTB25, ZBTB40, ZC3H3, ZFPI61, ZFP36L1, ZFP36L2, ZHX2, ZMYM5, ZNF136, ZNF148, ZNF318, ZNF350, ZNF512B, ZNF609, ZNF652, ZNF83, ZNF862, and ZNF91. In some embodiments, the GeneSetScore (Up resting vs. Down activated) is determined using RNA-seq, for example, single-cell RNA-seq (scRNA-seq), for example, as exemplified in Example 7 with respect to FIG. 24D. In some embodiments, the GeneSetScore (Up resting vs. Down activated) is calculated by taking the mean log normalized gene expression value of all of the genes in the gene set.

As used herein, the term “GeneSetScore (Progressively up in memory differentiation)” of a cell refers to a score that reflects the stage of the cell in memory differentiation. A higher GeneSetScore (Progressively up in memory differentiation) indicates an increasing late memory T cell phenotype, whereas a lower GeneSetScore (Progressively up in memory differentiation) indicates an increasing early memory T cell phenotype. In some embodiments, the GeneSetScore (Up autophagy) is determined by measuring the expression of one or more genes that are up-regulated during memory differentiation, for example, one or more genes selected from the group consisting of MTCH2, RAB6C, KIAA0195, SETD2, C2orf24, NRD1, GNA13, COPA, SELT, TNIP1, CBFA2T2, LRP10, PRKCI, BRE, ANKS1A, PNPLA6, ARL6IP1, WDFY1, MAPK1, GPR153, SHKBP1, MAP1LC3B2, PIP4K2A, HCN3, GTPBP1, TLN1, C4orf34, KIF3B, TCIRG1, PPP3CA, ATG4D, TYMP, TRAF6, C17orf76, WIPF1, FAM108A1, MYL6, NRM, SPCS2,

GGT3P, GALKI, CLIP4, ARL4C, YWHAQ, LPCAT4, ATG2A, IDS, TBC1D5, DMPK, ST6GALNAC6, REEP5, ABHD6, KIAA0247, EMB, TSEN54, SPIRE2, PIWIL4, ZSCAN22, ICAM1, CHD9, LPIN2, SETD8, ZC3H12A, ULBP3, IL15RA, HLA-DQB2, LCP1, CHP, RUNX3, TMEM43, REEP4, MEF2D, ABL1, TMEM39A, PCBP4, PLCD1, CHST12, RASGRP1, C1orf58, C11orf63, C6orf129, FHOD1, DKFZp434F142, PIK3CG, ITPR3, BTG3, C4orf50, CNNM3, IFI16, AK1, CDK2AP1, REL, BCL2L1, MVD, TTC39C, PLEKHA2, FKBPI1, EML4, FANCA, CDCA4, FUCA2, MFSD10, TBCD, CAPN2, IQGAP1, CHST11, PIK3R1, MYOSA, KIR2DL3, DLG3, MXD4, RALGD5, S1PR5, WSB2, CCR3, TIPARP, SP140, CD151, SOX13, KRTAP5-2, NF1, PEA15, PARP8, RNF166, UEVLD, LIMK1, CACNB1, TMX4, SLC6A6, LBA1, SV2A, LLGL2, IRF1, PPP2R5C, CD99, RAPGEF1, PPP4R1, OSBPL7, FOXP4, SLA2, TBC1D2B, ST7, JAZF1, GGA2, PI4K2A, CD68, LPGAT1, STX11, ZAK, FAM160B1, RORA, C8orf80, APOBEC3F, TGFB1, DNAJC1, GPR114, LRP8, CD69, CMIP, NAT13, TGFB1, FLJ00049, ANTXR2, NR4A3, IL12RB1, NTNG2, RDX, MLLT4, GPRIN3, ADCY9, CD300A, SCDS, ABI3, PTPN22, LGALS1, SYTL3, BMPR1A, TBK1, PMAIP1, RASGEF1A, GCNT1, GABARPL1, STOM, CALHM2, ABCA2, PPP1R16B, SYNE2, PAM, C12orf75, CLCF1, MXRA7, APOBEC3C, CLSTN3, ACOT9, HIP1, LAG3, TNFAIP3, DCBLD1, KLF6, CACNB3, RNF19A, RAB27A, FADS3, DLG5, APOBEC3D, TNFRSF1B, ACTN4, TBKBP1, ATXN1, ARAP2, ARHGEF12, FAM53B, MAN1A1, FAM38A, PLXNC1, GRLF1, SRGN, HLA-DRB5, B4GALT5, WIP1, PTPRJ, SLFN11, DUSP2, ANXA5, AHNAK, NEO1, CLIC1, EIF2C4, MAP3K5, IL2RB, PLEKHG1, MYO6, GTDC1, EDARADD, GALM, TARP, ADAM8, MSC, HNRPLL, SYT11, ATP2B4, NHSL2, MATK, ARHGAP18, SLFN12L, SPATS2L, RAB27B, PIK3R3, TP53INP1, MBOAT1, GYG1, KATNAL1, FAM46C, ZC3HAV1L, ANXA2P2, CTNNA1, NPC1, C3AR1, CRIM1, SH2D2A, ERN1, YPEL1, TBX21, SLC1A4, FASLG, PHACTR2, GALNT3, ADRB2, PIK3AP1, TLR3, PLEKHA5, DUSP10, GNAO1, PTGDR, FRMD4B, ANXA2, EOMES, CADM1, MAF, TPRG1, NBEAL2, PPP2R2B, PELO, SLC4A4, KLRF1, FOSL2, RGS2, TGFB3, PRF1, MYO1F, GAB3, C17orf66, MICAL2, CYTH3, TOX, HLA-DRA, SYNE1, WEE1, PYHINI, F2R, PLD1, THBS1, CD58, FAS, NETO2, CXCR6, ST6GALNAC2, DUSP4, AUTS2, C1orf21, KLIG1, TNIP3, GZMA, PRR5L, PRDM1, ST8SIA6, PLXND1, PTPRM, GFPT2, MYBL1, SLAMP7, FLJ16686, GNLY, ZEB2, CST7, ILI8RAP, CCL5, KLRD1, and KLRB1. In some embodiments, the GeneSetScore (Progressively up in memory differentiation) is determined using RNA-seq, for example, single-cell RNA-seq (scRNA-seq), for example, as exemplified in Example 7 with respect to FIG. 26B. In some embodiments, the GeneSetScore (Progressively up in memory differentiation) is calculated by taking the mean log normalized gene expression value of all of the genes in the gene set.

As used herein, the term “GeneSetScore (Up TEM vs. Down TN)” of a cell refers to a score that reflects the degree at which the cell shows an effector memory T cell (TEM) phenotype vs. a naïve T cell (TN) phenotype. A higher GeneSetScore (Up TEM vs. Down TN) indicates an increasing TEM phenotype, whereas a lower GeneSetScore (Up TEM vs. Down TN) indicates an increasing TN phenotype. In some embodiments, the GeneSetScore (Up TEM vs. Down TN) is determined by measuring the expression of one or more genes that are up-regulated in TEM cells and/or

down-regulated in TN cells, for example, one or more genes selected from the group consisting of MYOSA, MXD4, STK3, S1PR5, GLCCI1, CCR3, SOX13, KRTAP5-2, PEA15, PARP8, RNF166, UEVLD, LIMK1, SLC6A6, SV2A, KPNA2, OSBPL7, ST7, GGA2, PI4K2A, CD68, ZAK, RORA, TGFB1, DNAJC1, JOSD1, ZFYVE28, LRP8, OSBPL3, CMIP, NAT13, TGFB1, ANTXR2, NR4A3, RDX, ADCY9, CHN1, CD300A, SCD5, PTPN22, LGALS1, RASGEF1A, GCNT1, GLUL, ABCA2, CLDND1, PAM, CLCF1, MXRA7, CLSTN3, ACOT9, METRNL, BMPR1A, LRIG1, APOBEC3G, CACNB3, RNF19A, RAB27A, FADS3, ACTN4, TBKBP1, FAM53B, MAN1A1, FAM38A, GRLF1, B4GALT5, WIP1, DUSP2, ANXA5, AHNAK, CLIC1, MAP3K5, ST8SIA1, TARP, ADAM8, MATK, SLFN12L, PIK3R3, FAM46C, ANXA2P2, CTNNA1, NPC1, SH2D2A, ERN1, YPEL1, TBX21, STOM, PHACTR2, GBP5, ADRB2, PIK3AP1, DUSP10, PTGDR, EOMES, MAF, TPRG1, NBEAL2, NCAPH, SLC4A4, FOSL2, RGS2, TGFB3, MYO1F, C17orf66, CYTH3, WEE1, PYHINI, F2R, THBS1, CD58, AUTS2, FAM129A, TNIP3, GZMA, PRR5L, PRDM1, PLXND1, PTPRM, GFPT2, MYBL1, SLAMP7, ZEB2, CST7, CCL5, GZMK, and KLRB1. In some embodiments, the GeneSetScore (Up TEM vs. Down TN) is determined using RNA-seq, for example, single-cell RNA-seq (scRNA-seq), for example, as exemplified in Example 7 with respect to FIG. 26C. In some embodiments, the GeneSetScore (Up TEM vs. Down TN) is calculated by taking the mean log normalized gene expression value of all of the genes in the gene set.

In the context of GeneSetScore values (e.g., median GeneSetScore values), when a positive GeneSetScore is reduced by 100%, the value becomes 0. When a negative GeneSetScore is increased by 100%, the value becomes 0. For example, in FIG. 25A, the median GeneSetScore of the Day1 sample is -0.084; the median GeneSetScore of the Day9 sample is 0.035; and the median GeneSetScore of the input sample is -0.1. In FIG. 25A, increasing the median GeneSetScore of the input sample by 100% leads to a GeneSetScore value of 0; and increasing the median GeneSetScore of the input sample by 200% leads to a GeneSetScore value of 0.1. In FIG. 25A, decreasing the median GeneSetScore of the Day9 sample by 100% leads to a GeneSetScore value of 0; and decreasing the median GeneSetScore of the Day9 sample by 200% leads to a GeneSetScore value of -0.035.

As used herein, the term “bead” refers to a discrete particle with a solid surface, ranging in size from approximately 0.1 pm to several millimeters in diameter. Beads may be spherical (for example, microspheres) or have an irregular shape. Beads may comprise a variety of materials including, but not limited to, paramagnetic materials, ceramic, plastic, glass, polystyrene, methylstyrene, acrylic polymers, titanium, latex, Sepharose™, cellulose, nylon and the like. In some embodiments, the beads are relatively uniform, about 4.5 m in diameter, spherical, superparamagnetic polystyrene beads, for example, coated, for example, covalently coupled, with a mixture of antibodies against CD3 (for example, CD3 epsilon) and CD28. In some embodiments, the beads are Dynabeads®. In some embodiments, both anti-CD3 and anti-CD28 antibodies are coupled to the same bead, mimicking stimulation of T cells by antigen presenting cells. The property of Dynabeads® and the use of Dynabeads® for cell isolation and expansion are well known in the art, for example, see, Neurauter et al., *Cell isolation and expansion using Dynabeads*, Adv Biochem Eng Biotechnol. 2007; 106:41-73, herein incorporated by reference in its entirety.

As used herein, the term "nanomatrix" refers to a nanostructure comprising a matrix of mobile polymer chains. The nanomatrix is 1 to 500 nm, for example, 10 to 200 nm, in size. In some embodiments, the matrix of mobile polymer chains is attached to one or more agonists which provide activation signals to T cells, for example, agonist anti-CD3 and/or anti-CD28 antibodies. In some embodiments, the nanomatrix comprises a colloidal polymeric nanomatrix attached, for example, covalently attached, to an agonist of one or more stimulatory molecules and/or an agonist of one or more costimulatory molecules. In some embodiments, the agonist of one or more stimulatory molecules is a CD3 agonist (for example, an anti-CD3 agonistic antibody). In some embodiments, the agonist of one or more costimulatory molecules is a CD28 agonist (for example, an anti-CD28 agonistic antibody).

In some embodiments, the nanomatrix is characterized by the absence of a solid surface, for example, as the attachment point for the agonists, such as anti-CD3 and/or anti-CD28 antibodies. In some embodiments, the nanomatrix is the nanomatrix disclosed in WO2014/048920A1 or as given in the MACS® GMP T Cell TransAct™ kit from Miltenyi Biotec GmbH, herein incorporated by reference in their entirety. MACS® GMP T Cell TransAct™ consists of a colloidal polymeric nanomatrix covalently attached to humanized recombinant agonist antibodies against human CD3 and CD28.

Various embodiments of the compositions and methods herein are described in further detail below. Additional definitions are set out throughout the specification.

#### Description

Provided herein are compositions of matter and methods of use for the treatment of a disease such as cancer using cells expressing one or more chimeric antigen receptors (CARs). In some embodiments, the invention provides a cell (e.g., an immune effector cell, e.g., T cell or NK cell) engineered to express one or more CARs, wherein the CAR T cell ("CART") or CAR NK cell exhibits an antitumor property.

In some embodiments, the cell expresses at least two CARs. In some embodiments, the cell expresses a first CAR that binds to a first antigen and a second CAR that binds to a second antigen. In some embodiments, the first antigen and the second antigen are different. In some embodiments, the first antigen is BCMA. In some embodiments, the first CAR is an anti-BCMA CAR comprising a CDR, VH, VL, scFv, or CAR sequence disclosed herein, e.g., a sequence disclosed in Tables 3-15, 19, 20, 22, and 26, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto, e.g., an anti-BCMA CAR disclosed herein. In some embodiments, the second antigen is CD19. In some embodiments, the second antigen is an anti-CD19 CAR comprising a CDR, VH, VL, scFv, or CAR sequence disclosed herein, e.g., a sequence disclosed in Tables 2, 19, and 22, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto, e.g., an anti-CD19 CAR disclosed herein. In some embodiments, the first CAR and the second CAR are expressed by nucleic acid sequences disposed on a single nucleic acid molecule. In some embodiments, the nucleic acid sequence encoding the first CAR and the nucleic acid sequence encoding the second CAR are separated by a nucleic acid sequence encoding a self-cleavage site, e.g., a P2A site, a T2A site, an E2A site, or an F2A site. In some embodiments, the cell is a cell expressing dual CARs disclosed herein. In some embodi-

ments, the first CAR and the second CAR are expressed by nucleic acid sequences disposed on separate nucleic acid molecules. In some embodiments, the cell is engineered using a co-transduction system disclosed herein.

In some embodiments, the cell expresses a CAR that binds to a first antigen and a second antigen. In some embodiments, the CAR is a diabody CAR disclosed herein. In some embodiments, the CAR comprises a binding domain that comprises a first VH (VH1), a first VL (VL1), a second VH (VH2), and a second VL (VL2). In some embodiments, the VH1 and VL1 bind to a first antigen and the VH2 and VL2 bind to a second antigen. In some embodiments, the VH1, VL1, VH2, and VL2 are arranged in the following configuration from the N-terminus to the C-terminus: VH1-optional linker 1 ("L1")-VH2-optional linker 2 ("L2")-VL2-optional linker 3 ("L3")-VL1, VH1-optional L1-VL2-optional L2-VH2-optional L3-VL1, VL1-optional L1-VH2-optional L2-VL2-optional L3-VH1, VL1-optional L1-VL2-optional L2-VH2-optional L3-VH1, VH2-optional L1-VH1-optional L2-VL1-optional L3-VL2, VH2-optional L1-VL1-optional L2-VH1-optional L3-VL2, VL2-optional L1-VH1-optional L2-VL1-optional L3-VH2; or VL2-optional L1-VL1-optional L2-VH1-optional L3-VH2.

In some embodiments, the CARs of the invention combine an antigen binding domain with an intracellular signaling molecule. For example, in some embodiments, the intracellular signaling molecule includes, but is not limited to, CD3-zeta chain, 4-1BB and CD28 signaling modules and combinations thereof.

Furthermore, the present invention provides CAR compositions and their use in medicaments or methods for treating, among other diseases, cancer or any malignancy or autoimmune diseases.

#### Chimeric Antigen Receptor (CAR)

The present invention provides immune effector cells (for example, T cells or NK cells) that are engineered to contain one or more CARs that direct the immune effector cells to cancer. This is achieved through an antigen binding domain on the CAR that is specific for a cancer associated antigen. There are two classes of cancer associated antigens (tumor antigens) that can be targeted by the CARs described herein: (1) cancer associated antigens that are expressed on the surface of cancer cells; and (2) cancer associated antigens that themselves are intracellular, however, fragments (peptides) of such antigens are presented on the surface of the cancer cells by MHC (major histocompatibility complex).

Accordingly, an immune effector cell, for example, obtained by a method described herein, can be engineered to contain a CAR that targets one of the following cancer associated antigens (tumor antigens): CD19, CD123, CD22, CD30, CD171, CS-1, CLL-1, CD33, EGFRvIII, GD2, GD3, BCMA, TN Ag, PSMA, ROR1, FLT3, FAP, TAG72, CD38, CD44v6, CEA, EPCAM, B7H3, KIT, IL-13Ra2, Mesothelin, IL-11Ra, PSCA, VEGFR2, LewisY, CD24, PDGFR-beta, PRSS21, SSEA-4, CD20, Folate receptor alpha, ERBB2 (Her2/neu), MUC1, EGFR, NCAM, Prostase, PAP, ELF2M, Ephrin B2, IGF-I receptor, CAIX, LMP2, gp100, bcr-abl, tyrosinase, EphA2, Fucosyl GM1, sLe, GM3, TGS5, HMWMAA, o-acetyl-GD2, Folate receptor beta, TEM1/CD248, TEM7R, CLDN6, TSHR, GPRC5D, CXORF61, CD97, CD179a, ALK, Plasminogen, PLAC1, GloboH, NY-BR-1, UPK2, HAVCR1, ADRB3, PANX3, GPR20, LY6K, OR51E2, TARP, WT1, NY-ESO-1, LAGE-1, legumain, HPV E6, E7, MAGE-A1, MAGE-A1, ETV6-

AML, sperm protein 17, XAGE1, Tie 2, MAD-CT-1, MAD-CT-2, Fos-related antigen 1, p53, p53 mutant, prostein, survivin and telomerase, PCTA-1/Galectin 8, MelanA/MART1, Ras mutant, hTERT, sarcoma translocation breakpoints, ML-IAP, ERG (TMPRSS2 ETS fusion gene), NA17, PAX3, Androgen receptor, Cyclin B1, MYCN, RhoC, TRP-2, CYP1B1, BORIS, SART3, PAX5, OY-TES1, LCK, AKAP-4, SSX2, RAGE-1, human telomerase reverse tran-

scriptase, RU1, RU2, intestinal carboxyl esterase, and mut hsp70-2.

Sequences of non-limiting examples of various components that can be part of a CAR molecule described herein are listed in Table 1, where "aa" stands for amino acids, and "na" stands for nucleic acids that encode the corresponding peptide.

TABLE 1

Sequences of various components of CAR		
SEQ ID NO	Description	Sequence
SEQ ID NO: 11	EF-1 $\alpha$ promoter (na)	CGTAGGGCTCCGGTGCCCCTCAGTGGGCAGAGCGCACATCGCC CACAGTCCCCGAGAAGTTGGGGGGAGGGTCGCAATGAAAC CGGTGCCAGAGAACGGTGGCGCGGGGTAAGACTGGAAAGTGA TGTCGTGACTGGCTCCGGCTTTTCCGAGGGTGGGGAGAAA CCGTATAAAGTGCAGTAGTCGCCGTGAACGTTCTTTCGCA ACGGGTTTGCCGCCAGAACACAGGTAAGTGCCTGCTGGITC CCCGGGGCTGGCCTCTTACGGGTTAGGCCCTTGCGTGCCTT GAATTACTCCACCTGGCTGCAGTACCTGATTCTTGATCCCGA GCTTCGGGTTGGAAGTGGGTGGAGAGTTCGAGGCTTGCCT TAAGGAGCCCCCTGCCCTCGTGTGAATTGAGGCCCTGGCTG GGGCTGGGGCCCGCGCTGCGAATCTGGCACCTTCGCGC CTGTCGCTGCTGCTTCGATAAGTCTCTAGCCATTAAAAATT GATGACCTGCTGCGACGCTTTTCTGGCAAGATACTCTGT AAATGCGGGCCAAGATCTGCAACTGTTGGTATTGGTTGGGG CCCGGGCGGCAGGGGGCCCGCGTCCAGGCCACATGTT GGGAGGGGGGGCTGGAGCGGGCACCGAGAAATGGGAC GGGGTAGCTCAAGCTGGCCGGCTGCTCTGGTGCCTGGCCT GCGCCGGCGTGTATGCCCGCGGCTGGCGCAAGGCTGGCCC GGTCGGCACCACTGGCTGAGGGAAAGATGGCCGCTCCCG GCCCTGCTGCAAGGGACCTCAAATGGAGGACGCCGGCTCG GAGAGCGGGCGGGTAGCTCACCCACAAAGGAAAGGGCT TTCCGTCCTCAGCGTCGCTCATGTGACTCCACGGAGTACCG GGCGCCGTCAGGCACCTCGATTAGTTCTCGAGCTTTGGAGT ACGTCGTCTTAAGTTGGGGAGGGTTTATGCGATGGAGT TTCCCCACACTGAGTGGGGAGACTGAAGTTAGGCCAGCTTG GCACTTGATGTAATTCTCTTGAAATTGCCCTTTTGAGTTG GATCTGGTTCATCTCAAGCCTCAGACAGTGGTCAAAGTT TTCTCCATTTCAGGTGCTGTA
SEQ ID NO: 1	Leader (aa)	MALPVTLALLPLALLLHAARP
SEQ ID NO: 12	Leader (na)	ATGGCCCTGCCTGTGACAGCCCTGCTGCTGCCTCTGGCTCTGCT GCTGCATGCCGCTAGACCC
SEQ ID NO: 199	Leader (na)	ATGGCCCTCCCTGTCACGCCCTGCTGCTCCGCTGGCTCTTCT GCTCCACGCCGCTGGCCC
SEQ ID NO: 351	Leader (aa)	MLLVTSLLCELPHPAFLIP
SEQ ID NO: 352	Leader (na)	ATGCTTCTCTGGTGACAAGCCTCTGCTCTGTGAGTTACCACA CCCAGCATTCTCTGATCCCA
SEQ ID NO: 353	Leader (na)	ATGCTGCTGCTGGTGACAGCCTGCTGCTGTGGAGCTGGCCC ACCCCGCCTTCTGCTGATCCCC
SEQ ID NO: 2	CD 8 hinge (aa)	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAHVTRGLDFACD
SEQ ID NO: 13	CD8 hinge (na)	ACACAGCAGGCCAGGCCGCGACCAACACCGGCCACC ATCGCGTCGCAGCCCTGTCCTGCGCCAGGGCGTGGCG CAGCGGGGGGGCGCAGTCACACGAGGGGGCTGGACTTCG CCTGTGAT
SEQ ID NO: 3	Ig4 hinge (aa)	ESKYGPCCPCPAPEFLGGPSVLFPPPKDLMISRTPEVTCVV DVSQEDPEVQFNWYVDGVVEVHNNAKTKPREEQFNSTYRVSVLT VLHQDWLNKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTL PSQEEMTKNQVSLTCLVKGFYPSDIAVEWESENQPNENYKTPPP LDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSL SLSLGKM

TABLE 1-continued

Sequences of various components of CAR		
SEQ ID NO	Description	Sequence
SEQ ID NO: 14	Ig4 hinge (na)	GAGAGCAAGTACGGCCCTCCCTGCCCTGCCCCCTTGCCCTGCCCG AGTTCTGGCGGACCCAGCGTGTTCCTGTTCCTCCCCCAAGGC CAAGGACACCCGTATGATCAGCGGACCCCGAGGTGACCTGT GTGGTGTGGACGCTGTCCCAGGAGACCCCGAGGTGACAGTCA ACTGGTACGTGACGGCGTGGAGGTGACAAAGCCAAGACCA AGCCCCCGGAGGAGCAGTTCAATAGCACCTACCGGGTGGTGT CCGTGCTGACCGTGTGACCAGGACTGGCTGAACCGCAAGG AATACAAGTGTAAAGGTCTCAACAAAGGGCTGCCAGCAGCA TCGAGAAAACCATCAGCAAGGCCAACGGCCAGGCTCGGGAGC CCCAGGTGTACACCCCTGCCCTAGGCAAGAGGAGATGACCA AGAACCAAGGTGTCCCTGACCTGCCTGGTGAAGGGCTCTACCC CAGCGACATCGCCGCTGGAGTGGAGAGCAACGGCACCCGA GAACAACATAAGAACACCCCCCTGTGCTGGACAGCGACAGG CAGCTCTCTCTGTACAGCGGCTGACCGTGGACAAGAGCCGG TGGCAGGAGGCAACGCTTTAGCTCTCGTGTGACGAGG CCCTGACAACCACTACACCCAGAACAGGCTGAGCCTGTCCCT GGCAAGATG
SEQ ID NO: 4	IgD hinge (aa)	RWPESPDKAQASSVPTAQPKQAEGLAKATTAPATRTRNTRGRGEEK KKEKEKEEQQERETKTPECPSTSHTQPLGVYLLTPAVQDLWLRDKA TFTCFVVGSDLKDAHLTWEVAGKVTGGVEEGLLERHSNGSQSQ HSRLTLPRSLWNAGTSVTCTLNHPSLPPQRMLAREPAQAPVKL SLNLASSDPPEAAASWLCEVSGFSPNNILLMWLEDQREVNTSGF APARPPQPQPGSTTFWAWSVLRVPAPPSPQPATYTCVVSHEDSRTL LNASRSRLEVSYVTDH
SEQ ID NO: 15	IgD hinge (na)	AGGTGGCCCGAAGTCCAAGGCCAGGCATCTAGTGTCC CTGCACAGCCCCAGGCAGAAGGCAGCTAGCAAAGCTACTA CTGCACCTGCACTACCGCAATACTGGCCGTGGCGGGAGG AGAAGAAAAGGAGAAGAGAAAAGAGAACAGGAAGAGAGG GAGACCAAGACCCCTGAATGTCCATCCATACCCAGCCGTGG GCGTCTATCTTGACTCCCGCAGTACAGGACTTGTGGCTTAG AGATAAGGGCACCTTACATGTTCTCGTGGCTTGACCTG AAGGATGGCCATTGACTGGAGGTTGCTGGAGGCCATTCAATG GCTCTAGAGCCAGCAGCAACTAACACTCACCTTCCGAGATCC GTGGACGGGGGACCTCTGTACATGTTACTCTAAATCATCCT AGCCTGGCCCCACAGGCTGTAGTGGCCCTAGAGAGCCAGCG CCCAGGCCAGGTTAAGCTTAGCCTGAATCTGCTCCCCAGTAG TGATCCCCAGAGGCCAGCTGGCTCTTATGCGAAGTGTCC GGCTTAGGCCAACACTTGTCTATGCGTGGCTGGAGGACC AGCGAGAAGTGAACACAGCGGCCCTCGCTCCAGGCCGGCCCC CACCCAGCCGGTTTACACATTGGGCTGGAGTGTCTT AAGGGTCCCAGCACCACTAGCCCCAGGCCACATACACC TGTGTTGTGCCCCATGAAGATAGCAGGACCCCTGCTAAATGCTT CTAGGAGTCTGGAGGTTCTACGTGACTGACCAT
SEQ ID NO: 6	CD8 Transmembrane (aa)	IYIWAPLAGTCGVLLSLVITLYC
SEQ ID NO: 17	CD8 Transmembrane (na)	ATCTACATCTGGCGCCCTTGCCGGACTTGTGGGGTCCTC TCCTGTCACTGGTTATCACCTTACTGC
SEQ ID NO: 7	4-1BB intracellular domain (aa)	KRGRKKLLYIFKQPFMRPVQTTQEEEDGCSRFPEEEAGGCEL
SEQ ID NO: 18	4-1BB intracellular domain (na)	AAACGGGGCAGAAAGAAAACCTCTGTATATATTCAAACAACCA TTTATGAGACAGTACAAACTACTCAAGAGGAAGATGGCTGA GCTGCCATTTCAGAGAAGAAGAAGAGGAGGATGTGAACTG
SEQ ID NO: 8	CD27 (aa)	QRRKYRSNKGESPVEPAEPCRYSCPREEGSTIPIQEDYRKPEPAC SP
SEQ ID NO: 19	CD27 (na)	AGGAGTAAGAGGAGCAGGCTCTGCACAGTGTACTACATGAAC ATGACTCCCCGCCGCCGGGCCACCGCAAGCATTACCAAGC CCTATCCCCACCAACCGCAGTCGAGCCTATCGCTCC
SEQ ID NO: 9	CD3-zeta (aa) (Q/K mutant)	RVKFSSADAPAYKQCNQLYNELNLRREYDVLDKRRGRDP EMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRKGKH DGLYQLSTATKDTYDALHMQALPPR
SEQ ID NO: 20	CD3-zeta (na) (Q/K mutant)	AGAGTGAAGTTCAGCAGGAGGCGCAGACGCCCGCGTACAAG CAGGGCCAGAACAGCTCTATAACGAGCTCAATCTAGGACGA AGAGAGGAGTACGATTTTGACAAAGAGACGTGGCCGGGAC

TABLE 1-continued

Sequences of various components of CAR		
SEQ ID NO	Description	Sequence
		CCTGAGATGGGGAAAGCCGAGAAGGAAGAACCTCAGGAA GGCTGTACATGAACCTGCAGAAAAGATAAGATGGCGAGGCC TACAGTGAGATTGGGATGAAAGGCAGGCAGCGCCGGAGGGCAAG GGCACGATGGCCTTACCAAGGGTCTCAGTACAGCCACCAAGG ACACCTACGACGCCCTTCACATGCAGGCCCTGCCCTCGC
10	SEQ ID NO: CD3-zeta (aa) (NCBI Reference Sequence NM_000734.3)	RVKFSRSADAPAYQQQNLQYELNLRREYDVLDRKRRGRDP EMGGKPRRKNPQEGLYNELOQDKMAEAYSEIGMKGERRRKGH DGLYQGLSTATKDTYDALHMQLALPPR
21	SEQ ID NO: CD3-zeta (na) (NCBI Reference Sequence NM_000734.3)	AGAGTGAAGTTTCAGCAGGAGCGCAGACGCCCGCGTACAG CAGGGCCAGAACCGCTCTATAACGAGCTCAATCTAGGACGA AGAGAGGACTACGATGTTTGGACAAGAGACGTGGCGGGAC CTGAGATGGGGAAAGCCGAGAAGGAAGAACCTCAGGAA GGCTGTACATGAACCTGCAGAAAAGATAAGATGGCGAGGCC TACAGTGAGATTGGGATGAAAGGCAGGCAGCGCCGGAGGGCAAG GGCACGATGGCCTTACCAAGGGTCTCAGTACAGCCACCAAGG ACACCTACGACGCCCTTCACATGCAGGCCCTGCCCTCGC
36	SEQ ID NO: CD28 Intracellular domain (amino acid sequence)	RSKRSLLHSDDYMNMTPRPGPTRKHYQPYAPPDFAAYRS
37	SEQ ID NO: CD28 Intracellular domain (nucleotide sequence)	AGGAGTAAGAGGAGCAGGCTCCTGCACAGTGACTACATGAAC ATGACTCCCCGCCGCCGGCCACCCCAAGCATTACCAAGC CCTATGCCACCACGCGACTTCGCAGCCTATCGCTCC
38	SEQ ID NO: ICOS Intracellular domain (amino acid sequence)	T K K K Y S S S V H D P N G E Y M F M R A V N T A K K S R L T D V T L
39	SEQ ID NO: ICOS Intracellular domain (nucleotide sequence)	ACAAAAAAAGAAGTATTCATCCAGTGTGCACGACCTAACGGT GAATACATGTTCATGAGAGCAGTGAACACAGCCAAAATCC AGACTCACAGATGTGACCTA
5	SEQ ID NO: GS hinge/linker (aa)	GGGSGGGGS
16	SEQ ID NO: GS hinge/linker (na)	GGTGGCGGAGGTTCTGGAGGTGGAGGTTCC
40	SEQ ID NO: GS hinge/linker (na)	GGTGGCGGAGGTTCTGGAGGTGGAGGTTCC
25	SEQ ID NO: linker	GGGS
26	SEQ ID NO: linker	(Gly-Gly-Gly-Ser)n, where n = 1-6, for example, GGGSGGGGS GGGSAGGGGS GGGSGGGGS
27	SEQ ID NO: linker	GGGGSGGGGGGGGGGGGGGG
28	SEQ ID NO: linker	GGGGSGGGGGGGGGGG
29	SEQ ID NO: linker	GGGS
41	SEQ ID NO: linker	(Gly-Gly-Gly-Ser)n where n is a positive integer equal to or greater than 1
42	SEQ ID NO: linker	(Gly-Gly-Gly-Ser)n, where n = 1-10, for example, GGGSGGGSGG GSGGGSGGGGS GGGSGGGSGG GSGGGSGGGGS
43	SEQ ID NO: linker	GSTSGSGKPGSGEGSTKG
30	SEQ ID NO: poly(A)	(A) <sub>5000</sub> This sequence may encompass 50-5000 adenines.
31	SEQ ID NO: polyT	(T) <sub>100</sub>
	SEQ ID NO: polyT	(T) <sub>5000</sub>

TABLE 1-continued

In some embodiments the antigen binding domain comprises the extracellular domain, or a counter-ligand binding fragment thereof, of molecule that binds a counterligand on the surface of a target cell.

The immune effector cells can comprise a recombinant DNA construct comprising sequences encoding a CAR, wherein the CAR comprises an antigen binding domain (for example, antibody or antibody fragment, TCR or TCR fragment) that binds specifically to a tumor antigen, for example, a tumor antigen described herein, and an intracellular signaling domain. The intracellular signaling domain can comprise a costimulatory signaling domain and/or a primary signaling domain, for example, a zeta chain. As described elsewhere, the methods described herein can include transducing a cell, for example, from the population of T regulatory-depleted cells, with a nucleic acid encoding a CAR, for example, a CAR described herein.

In some embodiments, a CAR comprises a scFv domain, wherein the scFv may be preceded by an optional leader sequence such as provided in SEQ ID NO: 1, and followed by an optional hinge sequence such as provided in SEQ ID NO:2 or SEQ ID NO:36 or SEQ ID NO:38, a transmembrane region such as provided in SEQ ID NO:6, an intracellular signaling domain that includes SEQ ID NO:7 or SEQ ID NO:16 and a CD3 zeta sequence that includes SEQ ID

NO:9 or SEQ ID NO:10, for example, wherein the domains are contiguous with and in the same reading frame to form a single fusion protein.

In some embodiments, an exemplary CAR constructs comprise an optional leader sequence (for example, a leader sequence described herein), an extracellular antigen binding domain (for example, an antigen binding domain described herein), a hinge (for example, a hinge region described herein), a transmembrane domain (for example, a transmembrane domain described herein), and an intracellular stimulatory domain (for example, an intracellular stimulatory domain described herein). In some embodiments, an exemplary CAR construct comprises an optional leader sequence (for example, a leader sequence described herein), an extracellular antigen binding domain (for example, an antigen binding domain described herein), a hinge (for example, a hinge region described herein), a transmembrane domain (for example, a transmembrane domain described herein), an intracellular costimulatory signaling domain (for example, a costimulatory signaling domain described herein) and/or an intracellular primary signaling domain (for example, a primary signaling domain described herein).

65 An exemplary leader sequence is provided as SEQ ID NO: 1. Further exemplary leaders include those provided in SEQ ID NO: 351 or encoded by SEQ ID NOs: 352 or 353.

An exemplary hinge/spacer sequence is provided as SEQ ID NO: 2 or SEQ ID NO:36 or SEQ ID NO:38. An exemplary transmembrane domain sequence is provided as SEQ ID NO:6. An exemplary sequence of the intracellular signaling domain of the 4-1BB protein is provided as SEQ ID NO: 7. An exemplary sequence of the intracellular signaling domain of CD27 is provided as SEQ ID NO:16. An exemplary CD3zeta domain sequence is provided as SEQ ID NO: 9 or SEQ ID NO:10.

In some embodiments, the immune effector cell comprises a recombinant nucleic acid construct comprising a nucleic acid molecule encoding a CAR, wherein the nucleic acid molecule comprises a nucleic acid sequence encoding an antigen binding domain, wherein the sequence is contiguous with and in the same reading frame as the nucleic acid sequence encoding an intracellular signaling domain. An exemplary intracellular signaling domain that can be used in the CAR includes, but is not limited to, one or more intracellular signaling domains of, for example, CD3-zeta, CD28, CD27, 4-1BB, and the like. In some instances, the CAR can comprise any combination of CD3-zeta, CD28, 4-1BB, and the like.

The nucleic acid sequences coding for the desired molecules can be obtained using recombinant methods known in the art, such as, for example by screening libraries from cells expressing the nucleic acid molecule, by deriving the nucleic acid molecule from a vector known to include the same, or by isolating directly from cells and tissues containing the same, using standard techniques. Alternatively, the nucleic acid of interest can be produced synthetically, rather than cloned.

Nucleic acids encoding a CAR can be introduced into the immune effector cells using, for example, a retroviral or lentiviral vector construct.

Nucleic acids encoding a CAR can also be introduced into the immune effector cell using, for example, an RNA construct that can be directly transfected into a cell. A method for generating mRNA for use in transfection involves in vitro transcription (IVT) of a template with specially designed primers, followed by poly(A) addition, to produce a construct containing 3' and 5' untranslated sequence ("UTR") (for example, a 3' and/or 5' UTR described herein), a 5' cap (for example, a 5' cap described herein) and/or Internal Ribosome Entry Site (IRES) (for example, an IRES described herein), the nucleic acid to be expressed, and a poly(A) tail, typically 50-2000 bases in length (for example, described in the Examples, for example, SEQ ID NO:35). RNA so produced can efficiently transfect different kinds of cells. In some embodiments, the template includes sequences for the CAR. In some embodiments, an RNA CAR vector is transduced into a cell, for example, a T cell by electroporation.

#### Antigen Binding Domain

In some embodiments, a plurality of the immune effector cells, for example, the population of T regulatory-depleted cells, include a nucleic acid encoding a CAR that comprises a target-specific binding element otherwise referred to as an antigen binding domain. The choice of binding element depends upon the type and number of ligands that define the surface of a target cell. For example, the antigen binding domain may be chosen to recognize a ligand that acts as a cell surface marker on target cells associated with a particular disease state. Thus, examples of cell surface markers that may act as ligands for the antigen binding domain in a CAR described herein include those associated with viral, bacterial and parasitic infections, autoimmune disease and cancer cells.

In some embodiments, the portion of the CAR comprising the antigen binding domain comprises an antigen binding domain that targets a tumor antigen, for example, a tumor antigen described herein.

The antigen binding domain can be any domain that binds to the antigen including but not limited to a monoclonal antibody, a polyclonal antibody, a recombinant antibody, a human antibody, a humanized antibody, and a functional fragment thereof, including but not limited to a single-domain antibody such as a heavy chain variable domain (VH), a light chain variable domain (VL) and a variable domain (VHH) of camelid derived nanobody, and to an alternative scaffold known in the art to function as antigen binding domain, such as a recombinant fibronectin domain, a T cell receptor (TCR), or a fragment thereof, for example, single chain TCR, and the like. In some instances, it is beneficial for the antigen binding domain to be derived from the same species in which the CAR will ultimately be used in. For example, for use in humans, it may be beneficial for the antigen binding domain of the CAR to comprise human or humanized residues for the antigen binding domain of an antibody or antibody fragment.

#### CD19 CAR

In some embodiments, the CAR-expressing cell described herein is a CD19 CAR-expressing cell (for example, a cell expressing a CAR that binds to human CD19).

In some embodiments, the antigen binding domain of the CD19 CAR has the same or a similar binding specificity as the FMC63 scFv fragment described in Nicholson et al. Mol. Immun. 34 (16-17): 1157-1165 (1997). In some embodiments, the antigen binding domain of the CD19 CAR includes the scFv fragment described in Nicholson et al. Mol. Immun. 34 (16-17): 1157-1165 (1997).

In some embodiments, the CD19 CAR includes an antigen binding domain (for example, a humanized antigen binding domain) according to Table 3 of WO2014/153270, incorporated herein by reference. WO2014/153270 also describes methods of assaying the binding and efficacy of various CAR constructs.

In some embodiments, the parental murine scFv sequence is the CAR19 construct provided in PCT publication WO2012/079000 (incorporated herein by reference). In some embodiments, the anti-CD19 binding domain is a scFv described in WO2012/079000.

In some embodiments, the CAR molecule comprises the fusion polypeptide sequence provided as SEQ ID NO: 12 in PCT publication WO2012/079000, which provides an scFv fragment of murine origin that specifically binds to human CD19.

In some embodiments, the CD19 CAR comprises an amino acid sequence provided as SEQ ID NO: 12 in PCT publication WO2012/079000.

In some embodiments, the amino acid sequence is: Diqmtqtsslsaslgdrvtiscrasqdskly-  
lnwyqqkpdgtvkliiyhtsrlhsgvpsrfgsgsgtdysltisnleqed-  
atyfcqqgn tlpytfggktleitggsgggsgggsevklgesgpqlvap-  
sqslsvctvsgvslpdygvswirqpprkglewlgviwgsettyynsalksr  
ltiikdnksqvfkmnslqtdtaiyy-  
cakhyyyggsyamdywgqqtstvsssttpaprppptaptiasqplslrpear-  
paaggavhtrgldfa cdiyiwaplagtcvgllslvitlyckgrkrkllly-  
ifkqpfmrvpqttqeegcscrfpeeeeggcelrvkfsrsadapaykqgqnqlqy-  
nefnlgrre  
eydvlkdrrgdpmeggkprknpgeglynelqdkmaeaysei-  
gmkgerrrgkghdglyqlstatkdtydalmqalpr (SEQ ID NO:  
292), or a sequence substantially homologous thereto.

In some embodiments, the CD19 CAR has the USAN designation TISAGENLECLEUCEL-T. In embodiments,

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CTL019 is made by a gene modification of T cells is mediated by stable insertion via transduction with a self-inactivating, replication deficient Lentiviral (LV) vector containing the CTL019 transgene under the control of the EF-1 alpha promoter. CTL019 can be a mixture of transgene positive and negative T cells that are delivered to the subject on the basis of percent transgene positive T cells.

In other embodiments, the CD19 CAR comprises an antigen binding domain (for example, a humanized antigen binding domain) according to Table 3 of WO2014/153270, incorporated herein by reference.

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Humanization of murine CD19 antibody is desired for the clinical setting, where the mouse-specific residues may induce a human-anti-mouse antigen (HAMA) response in patients who receive CART19 treatment, i.e., treatment with T cells transduced with the CAR19 construct. The production, characterization, and efficacy of humanized CD19 CAR sequences is described in International Application WO2014/153270 which is herein incorporated by reference in its entirety, including Examples 1-5 (p. 115-159).

10 In some embodiments, the CAR molecule is a humanized CD19 CAR comprising the amino acid sequence of:

(SEQ ID NO: 293)  
 EIVMTQSPATLSLSPGERATLSCRASQDISKYLNWYQQKPGQAPRLLIYHTSRLHSGIPARFSGS  
 GSGTDYTLTISSLQPEDFAVYFCQQGNTLPYTFGQGTKEIKGGGGSGGGSGGGGSQVQLQESG  
 PGLVKPSETLSLTCTVSGVSLPDYGVSWIRQPPGKLEWIGIVIWGSETTYQSSLKSRVTISKDN  
 SKNQVSLKLSSVTAADTAVYYCAKHYYYGGSYAMDYWGQGTLTVSS

20

In some embodiments, the CAR molecule is a humanized CD19 CAR comprising the amino acid sequence of:

(SEQ ID NO: 294)  
 EIVMTQSPATLSLSPGERATLSCRASQDISKYLNWYQQKPGQAPRLLIYHTSRLHSGIPARFSGS  
 GSGTDYTLTISSLQPEDFAVYFCQQGNTLPYTFGQGTKEIKGGGGSGGGSGGGGSQVQLQESG  
 PGLVKPSETLSLTCTVSGVSLPDYGVSWIRQPPGKLEWIGIVIWGSETTYQSSLKSRVTISKDN  
 SKNQVSLKLSSVTAADTAVYYCAKHYYYGGSYAMDYWGQGTLTVSSTTTPAPRPTPAPTIASQ  
 PLSLRPEACRPAAAGGAHVTRGLDFACDIYIWIAPLAGTCGVLLSLLVITLYCKRGRKKLLYIFKQP  
 FMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREYDVLDK  
 RRGDRPEMGGKPRRKNPQEGLYNELQDKMAEAYSEIGMKGERRGKGHDGLYQGLSTATKDTYD  
 ALHMQALPPR

In some embodiments, the CAR molecule is a humanized CD19 CAR comprising the amino acid sequence of:

(SEQ ID NO: 349)  
MALPVTALLPLALLLHAARPEIIVMTQSPATLSLSPGERATLSCRASQDISKYLNWYQQKPGQAP  
 RLLIYHTSRLHSGIPARFSGSGSTDYTLTISSLQPEDFAVYFCQQGNTLPYTFGQGTKEIKGG  
 GGSGGGGSGGGGSQVQLQESGPGLVKPSETLSLTCTVSGVSLPDYGVSWIRQPPGKLEWIGIVI  
 GSETTYQSSLKSRVTISKDNSKNQVSLKLSSVTAADTAVYYCAKHYYYGGSYAMDYWGQGTLVT  
 VSSTTPAPRPTPAPTIAQSPLSLRPEACRPAAAGGAHVTRGLDFACDIYIWIAPLAGTCGVLLS  
 LVITLYCKRGRKKLLYIFKQPMPRVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYQQG  
 QNQLYNELNLGRREYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQDKMAEAYSEIGMKGER  
 RGKGHDGLYQGLSTATKDTYDALHMQALPPR

In some embodiments, the CAR molecule is a humanized CD19 CAR comprising the amino acid sequence of:

(SEQ ID NO: 350)  
 EIVMTQSPATLSLSPGERATLSCRASQDISKYLNWYQQKPGQAPRLLIYHTSRLHSGIPARFSGS  
 GSGTDYTLTISSLQPEDFAVYFCQQGNTLPYTFGQGTKEIKGGGGSGGGSGGGGSQVQLQESG  
 PGLVKPSETLSLTCTVSGVSLPDYGVSWIRQPPGKLEWIGIVIWGSETTYQSSLKSRVTISKDN

- continued

SKNQVSLKLSVTAAATAVYYCAKHYYYGGSYAMDYWGQGTLTVSSTTPAPRPPPTAPTIASQ  
 PLSLRPEACRPAAGGAHVTRGLDFACDIYIWAPLAGTCGVLLSLVITLYCKRGRKKLLYIFKQP  
 FMRPVQTTQEEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYQOGQNQLYNELNLGRREYDVLDK  
 RRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRGKGHDGLYQGLSTATKDTYD  
 ALHMQALPPR

Any known CD19 CAR, for example, the CD19 antigen binding domain of any known CD19 CAR, in the art can be used in accordance with the present disclosure. For example, LG-740; CD19 CAR described in the U.S. Pat. Nos. 8,399,645; 7,446,190; Xu et al., Leuk Lymphoma. 2013 54(2): 255-260(2012); Cruz et al., Blood 122(17):2965-2973 (2013); Brentjens et al., Blood, 118(18):4817-4828 (2011); Kochenderfer et al., Blood 116(20):4099-102 (2010); Kochenderfer et al., Blood 122 (25):4129-39(2013); and 16th Annu Meet Am Soc Gen Cell Ther (ASGCT) (May 15-18, Salt Lake City) 2013, Abst 10.

Exemplary CD19 CARs include CD19 CARs described herein or an anti-CD19 CAR described in Xu et al. Blood 123.24(2014):3750-9; Kochenderfer et al. Blood 122.25 (2013):4129-39, Cruz et al. Blood 122.17(2013):2965-73, NCT00586391, NCT01087294, NCT02456350, NCT00840853, NCT02659943, NCT02650999, NCT02640209, NCT01747486, NCT02546739, NCT02656147, NCT02772198, NCT00709033, NCT02081937, NCT00924326, NCT02735083, NCT02794246, NCT02746952, NCT01593696, NCT02134262, NCT01853631, NCT02443831, 10 NCT02277522, NCT02030834, NCT02030847, NCT02813837, NCT02529813, NCT02672501, NCT01840566, NCT02706405, NCT02146924, NCT01815749, NCT02208362, NCT02631044, NCT01860937, NCT02465983, NCT01493453, NCT01029366, NCT01044069, NCT02822326, NCT02132624, NCT02652910, NCT01626495, NCT00422383, NCT02794961, or NCT02456207, each of which is incorporated herein by reference in its entirety.

In some embodiments, CD19 CARs comprise a sequence, for example, a CDR, VH, VL, scFv, or full-CAR sequence, disclosed in Table 2, or a sequence having at least 80%, 85%, 90%, 95%, or 99% identity thereto.

TABLE 2

Amino acid sequences of exemplary anti-CD19 molecules		
SEQ ID NO	Region	Sequence
<u>CTL019</u>		
295	HCDR1 (Kabat)	DYGVS
296	HCDR2 (Kabat)	VIWGSETTYNSALKS
297	HCDR3 (Kabat)	HYYYGGSYAMDY
298	LCDR1 (Kabat)	RASQDISKYLN
299	LCDR2 (Kabat)	HTSRLHS
300	LCDR3 (Kabat)	QQGNTLPYT
301	CTL019 Full amino acid sequence	MALPVTALLPLALLHAARPDIQMTQTTSSLSASLGDRVVTISCRASQDIS KYLNWYQQKPDGTVKLLIYHTSRLHSGVPSPRFSGSGSGTDYSLTISNLEQ EDIATYFCQQGNTLPYTFFGGTKLEITGGGGSGGGGGGGSEVKLQES GPGLVAPSQSLSVTCTVSGVSLPDYGVSWIRQPPRKGLEWLGVIWGSET TYYNSALKSRLTIIKDNKSQVFLKMNSLQTDDTAIYYCAKHYYYGGSY AMDYWGQGTSVTVSSTTPAPRPPPTAPTIAQPLSLRPEACRPAAGGAV HTRGLDFACDIYIWAPLAGTCGVLLSLVITLYCKRGRKKLLYIFKQPFM RPVQTTQEEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYQOGQNQLYNE LNLRGREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEA YSEIGMKGERRGKGHDGLYQGLSTATKDTYDALHMQALPPR

TABLE 2 -continued

Amino acid sequences of exemplary anti-CD19 molecules		
SEQ ID NO	Region	Sequence
302	CTL019 Full nucleotide sequence	ATGGCCTTACCACTGACC CGCTTGCTCTGCCGCTGGCCTTGCTGCTC CACGCCGCCAGGCCGACATCCAGATGACACAGACTACATCCTCCCT GTCTGCCTCTCTGGGAGACAGAGTCACCATCAGTTGCAGGGCAAGTC AGGACATTAAGTAAATATTAAATTGGTATCAGCAGAAACCGAGATGGA ACTGTTAACCTCTGATCTACCATACATCAAGATTACACTCAGGAGTC CCATCAAGGGTTCACTGGCAGTGGGCTGGAACAGATTATCTCTCAC ATTAGCAACCTGGAGCAAGAAGATATTGCCACTTACTTTGCCAAC GGGTAATACGCTTCCGACAGTTCGGAGGGGGGACCAAGCTGGAGA TCACAGGTGGGGTGGCTCGGGCGGTGGTGGGTGGGGTGGCGGCGGA TCTGAGGTGAAACTGCAGGAGTCAGGACCTGGCTGGCTGGCGCCCTC ACAGAGCCTGCGTACATGCACTGTCAGGGGCTCATACCTACCG ACTATGGTGAAGCTGGATTGGCAAGCTCCACGAAAGGGTCTGGAG TGGTAAGGAGTAATATGGGAGTGAACACATACTATAATTTCAGC TCTCAATCCAGACTGACCATCATCAAGGACAACCTCAAGAGGCAAG TTTCTTAAATGAACAGTCTGCACACTGATGACACAGCATTACT ACTGTCGCAAACATTATTAACAGGTTGAGCTATGCTATGGACTACT GGGCCAACAGGAACCTCAGTCACCGTCTCCCAACCACGACGCCAGCG CCGCACCAACACCGGCCAACATCGCTCGCAGCCCCCTGTC CCTGCGCCAGAGGCGTGCAGGGCAGCGGGGGGGCGAGTCAG ACGAGGGGCTGGACTTCGCTGTATACATCTGGCGCCCTT GGCGGGACTTGTGGGCTCTCTGTACTGGTTATCACCTTTA CTGCAACAGGGCAGAAAAGAAACTCTGTATATATTCAAAACACAT TTATGAGACCAGTACAACACTACTCAAGAGGAAGATGGCTGAGTGC CGATTTCAGAAGAAGAAGAAGGAGGATGTAACCTGAGAGTGAAGT TCAGCAGGAGCGCAGACGCCCGCTACAAGCAGGGCCAGAACCA GCTCTATAACGAGCTAAATCTAGGAGAAGAGAGGAGTACGATGTT TGGACAAGAGACGTGGCCGGGACCTGAGATGGGGGAAAGCCGAG AAGGAAGAACCTCAGGAAGGCCTACAGTGAGATTGGGATGAAAGGGCAGCGCC GGAGGGCAAGGGCACAGATGCCCTTACCAAGGGCTCTCAGTACAGCC ACCAAGGACACCTACGACGCCCTCACATGCAGGCCCTGCCCTCGC
303	CTL019 scFv domain	DIQMTQTSSLASLGDRVTISCRASQDISKYLNWYQQKPDGTVKLLIYH TSRLHSGVPSPRSFGSGSGTDYSLTISNLEQEDIATYFCQQGNTLPYTFGGG TKLEITGGGGSGGGSGGGSEVKLQESGPGLVAPSQSLSVTCTVSGVSL PDYGVSWIRQPFRKGLEWLGVIWGSETTYNSALKSRLTIKDNSKSQVF LKMNSLQTDATIYYCAKHYYGGSYAMDYWGQGTSVTVSS
<b>Humanized CAR2</b>		
295	HCDR1 (Kabat)	DYGVS
304	HCDR2 (Kabat)	VIWGSETTYQSSLKS
297	HCDR3 (Kabat)	HYYYGGSYAMDY
298	LCDR1 (Kabat)	RASQDISKYLN
299	LCDR2 (Kabat)	HTSRLHS
300	LCDR3 (Kabat)	QQGNTLPYT
293	CAR2 scFv domain - aa (Linker is <u>underlined</u> )	EIVMTQSPATLSLSPGERATLSCRASQDISKYLNWYQQKPGQAPRLLIYH TSRLHSGIPARFSGSGSGTDYTLTISLQPEDFAVYFCQQGNTLPYTFGGG TKLEITGGGGSGGGSGGGSGGGSGVQLQESGPGLVKPSETLSLTCTVSGVS LPDYGVSWIRQPFRKGLEWLGVIWGSETTYQSSLKSRVTISKDNSKNQ VSLKLSSVTAADTAVYYCAKHYYGGSYAMDYWGQGTLTVSS
305	CAR2 scFv domain - nt	GAAATTGTGATGACCCAGTCACCCGCACTCTTAGCCTTCAACCGGT GAGCGCCAAACCTGTCCTGAGAGCCTCCAAGACATCTAAAAATA CCTTAATTGGTATCAACAGAACGCCGGACAGGCTCTGCCCTCTGAT CTACCAACACAGCCGGCTCCATTCTGAATCCCTGCCAGGTTCAAGCG GTAGCGGATCTGGGACCGACTACACCCCTACTATCAGCTCACTGCG CCAGAGGACTTCGCTCTATTCTGTCAGCAAGGGAACACCCCTGCC CTACACCTTGGACAGGGCACCAAGCTGAGATTAAGGTGGAGGTG GCAGCGGAGGGTGGCTCCGGCGTGGAGGAAGCCAGGTCAACT CCAAGAAAGCGGACCGGGTCTGTGAAGCCATCAGAAACTCTTCAC TGACTTGTACTGTGAGCGGAGTGTCTCTCCCAGATTACGGGTGTCTT GGATCAGACAGCCACCGGGGAAAGGTCTGGAATGGATGGAGTGTATT

TABLE 2-continued

TABLE 2-continued

## US 12,383,601 B2

105

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TABLE 2-continued

Amino acid sequences of exemplary anti-CD19 molecules			
SEQ ID NO	Region	Sequence	
358	VH	CAGGTCCAGCTGCAGGAATCGGGCCCAGGACTGGTGAAGCCTAGCGA GACCCTGCCCCTGACCTGCACAGTGAGCGCGTGTCCCTGCCGATT ACGGCGTGAGCTGGATCAGACAGGCCCCCTGGCAAGTGTCCTGGAGTGG ATCGGGCTGATCTGGGGCTCTGAGACACATACTATCAGTCCTCTCG AAGAGCAGGGTGACCATCTAAGGACAACAGCAAGAATCAGGTGT CCCTGAAGCTGAGCTCCGTGACCGCAGAGATAACGGCGTGTACTATT TGCGCCAAGCACTACTATTACGGCGGCTCTATGCTATGGATTATTGG GGGCAGGGCACTCTGGTCACTGTCTCATCA	
359	VH	CAGGTGCAGCTGCAGGAATCTGGACCCGACTGGTGAACCTAGTGA AACTCTGTCTCTGACTTGTACCGTCTCAGGGTCTCACTGCCAGACTA CGGGCGTCTCTGGATCAGACAGGCCCCCTGGCAAGTGTCCTGGAGTGG TCGGCGTGTCTGGGGCTCTGAGACACATACTATCAGTCCTCTCG AAGAGCAGGGTGACCATCTAAGGACAACAGCAAGAATCAGGTGT CCTGAAGCTGAGCTAGCGTGACCGCCGATACAGCCGTGTACTATT GTGCCAAGCACTACTATTACGGCGGCTCTATGCTATGGATTATTGG GGCCAGGGCACCTCTGGTCACTGTCTCATCA	
360	VH	CAGGTCCAGCTGCAGGAAAGCGGGCCCAGGACTGGTGAAGCCTAGCG AGACCTCTGCCCCTGACCTGCACAGTGAGCGCGTGTCCCTGCCGATT ACGGCGTGTCTGGATCAGACAGGCCCCCTGGCAAGTGTCCTGGAGTGG ATCGGGCTGATCTGGGGCTCTGAGACACATACTATCAGTCCTCTCG AAGTCAAGGTGACCATCTAAGGACAACAGCAAGAATCAGGTGT GCCTGAAGCTGAGCTCCGTGACCGCAGAGATAACGGCGTGTACTATT TGTGCCAAGCACTACTATTACGGCGGCTCTATGCTATGGATTATTGG GGGCAGGGCACTCTGGTCACTGTCTCATCA	
361	VH	CAGGTGCAGCTGCAGGAGAGCGGGCCCAGGACTGGTGAAGCCTTCGG AGACACTGTCTCTGACCTGTACAGTGAGCGCGTGTCCCTGCCGAC TACGGCGTGTCTGGATCAGACAGGCCACCTGGCAAGGGACTGGAGTGG GATCGGGCTGATCTGGGGCAGCAGACAGGACACATACTATCAGAGCTCCC TGAAGTCAAGGGTACCATCAGCAAGGACAACCTCAAGAATCAGGTGT GAGCTGAAGCTGTCAGCGTGACCGCCGATACAGCCGTGTACTATT ATTGCCCAAGCACTACTATTACGGCGGCTCTATGCTATGGATTACTGG GGGCAGGGCACCTCTGGTCACTGTCTCATCA	
362	VH	CAGGTGCAGCTGCAGGAGTCTGGCCCAAGGACTGGTGAAGCCTCTGA GACCCTGAGCTGACCTGCACAGTGAGCGCGTGTCCCTGCCGATT CGGCCTGTCCTGGATCAGACAGGCCACCTGGCAAGGGACTGGAGTGG TCGGCGTGTCTGGGGCTCTGAGACACATACTATCAGTCCTCTCG AAGAGCAGGGTACCATCTCAAGGACAACCTCAAGAATCAGGTGT CCTGAAGCTGTCCTCTGTGACCGCCGATACAGCCGTGTACTATT TGCCAAAGCACTACTATTACGGCGGCTCTATGCTATGGACTACTGG GCCAGGGCACCTCTGGTCACTGTCTCATCA	
363	VH	CAGGTGCAGCTGCAGGAGTCTGGCCCAAGGACTGGTGAAGCCTCTGA GACCCTGAGCTGACCTGCACAGTGAGCGCGTGTCCCTGCCGATT ACGGCGTGTCTGGATCAGACAGGCCACCTGGCAAGGGACTGGAGTGG ATCGGGCTGATCTGGGGCAGCAGACACATACTATCAGTCCTCTCG GAAGTCAAGGGTACCATCTCAAGGACAACCTCAAGAATCAGGTGT GCCTGAAGCTGAGCTCCGTGACCGCAGAGATAACGGCGTGTACTATT TGCGCCAAGCACTACTATTACGGCGGCTCTATGCTATGGACTACTGG GGGCAGGGCACCTCTGGTCACTGTCTCATCA	
364	VH	CAGGTGCAGCTGCAGGAGTCCGGCCCAAGGACTGGTGAAGCCTTCGA GACACTGTCTCTGACCTGTACAGTGTCGGCGTGTCCCTGCCGACTA CGGGCGTGTGGATCAGACAGGCCACCTGGCAAGGGACTGGAGTGG ATCGGGCTGATCTGGGGCTCTGAGACACATACTATCAGTCCTCTCG AAGAGCAGGGTACCATCAGCAAGGACAACCTCAAGAATCAGGTGT CCCTGAAGCTGAGCTCCGTGACCGCAGAGATAACGGCGTGTACTATT TGCGCCAAGCACTACTATTACGGCGGCTCTATGCTATGGATTACTGG GGGCAGGGCACCTCTGGTCACTGTCTCATCA	
365	VL	GAGATCGTGATGACCCAGAGCCCCAGGCCACACTGAGCCTGTCCCCAGG AGAGGAGGCCCCACACTGTCTGTAGAGCCAGGATATCTCCAAGT ATCTGAACCTGTACAGCAGAGCCCTGGACAGGCAACAGGCTGTG ATCTACACACACTCTAGACTGCACAGCGGATCCCTGCCAGGTTCT GGCAGGGCTCGGCACAGACTATACCTGACAACTCTAGCCTGCA GCCAGGGATTTCGCCGTGTACTTTGTGAGCAGGGCAAACTCTGCC ATACACCTTGGATGCGGAACAACTAGGAAATCAAG	
366	VL	GAAGATTGTGATGACCCAGTCCCCGCTACTCTGTCTCTGCCCCAGG GAACGGGCTACTCTGTCTTGTCGCGCTTCCCAGGATATTAGCAAGTAC CTGAACCTGTACAGCAGAGCCAGGACAGGCAGGCAACAGGCTGTG CTACACACCTCTGCCCTGCACAGCGGATCCCTGCCAGGTTCTGCC	

TABLE 2-continued

Amino acid sequences of exemplary anti-CD19 molecules			
SEQ ID NO	Region	Sequence	
		CAGCGGCTCCGGCACAGACTACACCCGTACAATCAGCTCCCTGCAGC CTGAGGATTTCGCCGTGTACTTTGCCAGCAGGGCAATACCTGCCAT ATACATTTGGCTGTGGCACCAAGCTGGAGATCAAG	
367	VL	GAGATCGTGTGATGACCCAGTCCCCAGCCACACTGAGCCCTGTCCCCAGG AGAGAGGCCACCCCTGCTTGAGACCCAGGATATCTCAAAGT ATCTGAACACTGGTACCCAGCAGAACGCCATGGACAGGGCCAAGGCTGCT ATCTACACACACTCTAGACTGCAAGCAGGCTACCCCTGCCAGGTTTC GGCAGCGGCTCCGGCACAGACTATACCCGTACAATCTAGCCTGCA GCCAGAGGATTTCGCCGTGTACTTTGCCAGCAGGGCAATACCTG ATACACCTTTGGATGCGGAACAAACTGGAAATCAAG	
368	VL	GAGATTGATGACCCAGTCCCCGCCCCACCTGAGCTGTGAGCCCCGG AGAACAGGCTACCCCTGAGTTGCCAGCTCCAGGACATTCCAAGT ACCTGAACACTGGTATCAGCAGAACGCCAGGACAGGGCCAAGGCTGCT GATCTACACACCTCTGCCGTGCAAGCGGCATCCCAGCACGGTTCTC TGGCAGCGGCTCCGGCACAGACTACACCCGTACAATCTAGCCTGCA AGCCTGAGGATTTCGCCGTGTACTTTGCCAGCAGGGCAATACCTG CCATATACATTTGGCTGTGGCACCAAGCTGGAGATCAAG	
369	VL	GAGATCGTGTGATGACCCAGTCCAGCCACACTGTCCTGTGAGCCCCAGG AGAGAGGCCACCCCTGCTTGCGCCAGCCAGGATATCTCAAAGT ATCTGAACACTGGTACCCAGCAGAACGCCAGGACAGGGCCAAGGCTGCT GATCTACACACCCAGCAGACTGCACTCCGGCATCCCTGCAAGGTTCTC CGGCTCTGGCAGCGGCACAGACTACACCCGTACAATCTAGCCTGCA AGCCGAGGATTTCGCCGTGTATTTCGCCAGCAGGGCAATACCTG CCTTACACATTTGGCCAGGGCACCAAGCTGGAGATCAAG	
370	VL	GAGATCGTGTGATGACCCAGAGCCACACTGAGCCCTGTCCCCAGG AGAGAGGCCACCCCTGAGCTGCAAGCCTCCAGGATATCTCAAAGT ATCTGAACACTGGTACCCAGCAGAACGCCAGGACAGGGCCAAGGCTGCT ATCTACACACCCAGCAGACTGCACTCCGGCATCCCTGCAAGGTTCTC GGCAGCGGCTCCGGCACAGACTACACCCGTACAATCTAGCCTGCA GCCTGAGGATTTCGCCGTGTATTTCGCCAGCAGGGCAATACCTG ATACACATTTGGCCAGGGCACCAAGCTGGAGATCAAG	
371	VL	GAGATCGTGTGATGACCCAGAGCCACACTGAGCCCTGTCCCCAGG AGAGAGGCCACCCCTGAGCTGCTGCCCTCCAGGATATCTCAAAGT ATCTGAACACTGGTACCCAGCAGAACGCCAGGACAGGGCCAAGGCTGCT GATCTACACACCCAGCAGACTGCACTCCGGCATCCCTGCAAGGTTCTC CGGCTCTGGCAGCGGCACAGACTACACCCGTACAATCTAGCCTGCA CAGCCGAGGATTTCGCCGTGTATTTCGCCAGCAGGGCAATACCTG GCCTTACACATTTGGCCAGGGCACCAAGCTGGAGATCAAG	
372	VL	GAGATCGTGTGATGACCCAGTCCAGCCACACTGAGCCCTGTCCCCAGG AGAGAGGCCACCCCTGCTTGCAAGCCTGGACAGGGCCAAGGCTGCT ATCTACACACCTCTAGACTGCAACGCCATCCCAGCACGGTTCTC TGGCAGCGGCTCCGGCACAGACTACACCCGTACAATCTAGCCTGCA AGCCTGAGGATTTCGCCGTGTATTTCGCCAGCAGGGCAATACCTG CATACACATTTGGCCAGGGCACCAAGCTGGAGATCAAG	
250	VH	QVQLQESGPGLVKPSETLSLTCTVSGVSLPDYGVSWIRQPPGKLEWIGV IWGSETTYQQSSLKSRVTISKDNNSKNQVSLKLSSVTAADTAVYYCAKY YYGGSYAMDWGQGTLTVVSS	
251	VL	EIVMTQSPATLSPGERATLSCRASQDISKYLNWYQQKPGQAPRLIYH TSRLHSGIPARFSGSGSGTDYTLTISSLQPEDFAVYFCQQGNTLPYTFQGQ TKLEIK	
331	VH	QVQLQESGPGLVKPSETLSLTCTVSGVSLPDYGVSWIRQPPGKLEWIGV IWGSETTYQQSSLKSRVTISKDNNSKNQVSLKLSSVTAADTAVYYCAKY YYGGSYAMDWGQGTLTVVSS	
332	VL	EIVMTQSPATLSPGERATLSCRASQDISKYLNWYQQKPGQAPRLIYH TSRLHSGIPARFSGSGSGTDYTLTISSLQPEDFAVYFCQQGNTLPYTFQGQ TKLEIK	
373	CAR 1 scFv	EIVMTQSPATLSPGERATLSCRASQDISKYLNWYQQKPGQAPRLIYH HSGIPARFSGSGSGTDYTLTISSLQPEDFAVYFCQQGNTLPYTFQGQTKLEIKG GGGGGGGGGGGGSVQLQESGPGLVKPSETLSLTCTVSGVSLPDYGVSWIRQ PGKGLEWIGVIGWSETTYSSLKSRVTISKDNNSKNQVSLKLSSVTAADTAVY CAKYYYGGSYAMDWGQGTLTVVSS	
374	CAR 3 scFv	qvqlqesgpglvkpsetlsltctvsgvslpdygvswirqppgkglewigviwgs ettyyssslksrvtiskdnnsknqvlklssvtaadtavyycahyyyggssyam	

TABLE 2-continued

TABLE 2-continued

TABLE 2-continued

Amino acid sequences of exemplary anti-CD19 molecules		
SEQ ID NO	Region	Sequence
	no leader	KGKHLCPSPLFPGPSKPPFWVLVVVGGVLACYSLLTVAFIIFWVRSKRSRLLHS DYMMNTPRPGPTRKHYQPYAPPDRFAYRSRVSRSADAPAYQQGNQLYNE LNLRGRRREYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQDKMAEAYSEIGMK GERRRGKGHDGLYQGLSTATKDTYDALHMQALP P
390	CAR A- CD19 scFv nucleotide; no leader	gacatccagatgacacagactacatccctccgtctgcctctctggagacaga gttccatcagtgcaggcaagttagcattttaaacttgcatttcaccatacatcaaggat cacttcaggatccatcaggatcgtggcgtggggctggaaacagattatttc cttcaccatcggacaaatggatcgttttttttttttttttttttttttttttttt ggtaatacgcttcgttacacgttggagggggactaagtggaaataacaggc tccacccctggatccggcaagccccgatctggcgaggatccacaaggcgag gtgaaaactcgaggatcgtggcgtggccctcaagagccgttcc gtcacatcgatgttcgtgggttcatttactccgactatggtaagctgg cgccagcccccacaaaagggtctggatggctggagtaatgggttagtga accacatactataattcagctccaaatccagactgaccatcatcaaggacaac tccaagagccaaatgttttttttttttttttttttttttttttttttttt atttactatgtgcacaaatattactacgggttagctatgtctatggactac tgggtcaagggaaacctcagtcacccgttccctca
391	CAR A- CD19 scFv amino acid sequence; no leader	DIQMTQTSSLSASLGDRVITSCRASQDISKYLNWYQQKPDGTVKLLIYHTSRL HSGVPSRFSGSGSTDYSLTISNLQEEDIATYFCQQGNTLPYFGGGTKLEITG STSGSGKPGSSEGESTKGEVVLQESGPGLVAPSLSVICTVSGVSLPDYGVSWI RQPPRKGLEWLGVIWGSETTYNSALKSRLTIIDNSKSQVFLKMNSLQTD IYYCAKHYGGSYAMDYWGQGTTSVTVSS
392	CAR B- full nucleotide sequence; with leader	ATGCTGCTGGTGTGACCAGCCTGCTGTGCGAGCTGCCAACCCGCC CTGCTGATCCCCGACATCCAGATGACCCAGACCCACTCCAGCCTGAGCGCC CTGGCGCAGGGTGACCATCAGCTGGCGCCAGGGCAGGACATCAGCAAGTAC CTGAATCTGGTATCAGCAGAGCCCGAACGGCCACCGTCAGGCTGATCTAC ACCCAGCCGGCTGCACAGCGCGTGTGCCAGCGTTAACGGCGCTCGGC ACCGACTACAGCCTGACCATCTCAACCTGGAACAGGAAGATACTGCCAC TTTTGGCAGCAGGGCAACACACTGGCTTACACCTTGGCGGGCAACAAAGCTG GAAATCACGGCCAGCAGCCTCCGGCAGCGGAAGCCTGGCAGCGCGAGGGCAGC ACCAAGGGCGAGGTGAAGCTGCGAGGAAAGCGGCCCTGGCTGGCCCC CAGAGCTGAGCGTGTACCTGCACCGTGTGAGCCTGAGCCTGCCCCACTAC GTGAGCTGGATCAGGGCCAGGGCTGGAAATGGCTGGCGTGTGATC TGGCCAGCAGACGACCACTACTACACAGCCCTGAAGACCCGGCTGACCATC ATCAAGGACAACAGCAAGGCCAGGTGTCTCTGAAGATGAACAGCCTGAGC GACGACACGCCATCTACTACTGCGCCAAGCCTACTACTACAGCGCGAGCTAC GCCATTGGACTACTGGGGCAGGGCACAGCGTGTACACAGGCTGAACCTGG TACGGGACCCCTGGCCCTTGTGCTTGTCTGGGTCTGGTGGTGGTGG GGCGTGTGGCTGTCTACAGCCTGCTGTGACCGCTGGCTTACATCATCT GTGAAACGGGGCAGAAAGAAACTCTGTATATATTCAACAAACCATTTTGAGA CCAGTACAAACTACTACAGAGGAAGATGGCTGTAGCTCCGATTTCCAGAAGAA GAAGAAGGGAGATGTGAACTCGGGTGAAAGTTACAGCAGAAGCGCCGAG GCCCTACAGCAGGGCCAGAATCAGCTGTACACAGGCTGAACCTGGCAGAAGG GAAGAGTACGACGCTCTGGATAAGCGGAGAGGCCGGACCTGAGATGGCG AAGCTCGGGAGAAGAACCCCCAGGAAGGGCTGTATAACGAACTGCAGAAAGAC AAGATGGCCAGGGCTGTATCAGGGCTGTACAGCGAGATCAGCAGGCGAG AAGGGCCACGACGGCCCTGTATCAGGGCTGTACAGCGAGGCGAGGCC GACGCCCTGCACATGCAGGCCCTGCCCGAAGG
393	CAR B- full transgene amino acid sequence; with leader	MLLVTLTSLLCLELPHPAFLLIPIDIQMKTQTSLSASLGDRVITSCRASQDISK YLNWYQQKPDGTVKLLIYHTSRLHSGVPSRFSGSGSTDYSLTISNLQEEDIATY FCQGNTLPYTPGGGKLEITGSTSISGKPGSSEGESTKGEVVLQESGPGLVAPS QLSLSVTCTVSGVSLPDYGVSWIRQPPRKGLEWLGVIWGSETTYNSALKSRL TIIDNSKSQVFLKMNSLQDTDAIYCAKHYGGSYAMDYWGQGTTSVTVSS YGPCCPCPMFWLVVVGGVLACSYLLTVAFIIFWVKRGRKL LLYIFKQP PVQJTQEEEDGCSRFPEEEEGGCELRVKFSRSADAPAYQQGNQLYNE NLNLGR EEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQDKMAEAYSEIGMK KGHDGLYQGLSTATKDTYDALHMQALP P
394	CAR B- CD19 scFv nucleotide sequence; with leader	ATGCTGCTGGTGTGACCAGCCTGCTGTGCGAGCTGCCAACCCGCC CTGCTGATCCCCGACATCCAGATGACCCAGACCCACTCCAGCCTGAGCGCC CTGGCGCAGGGTGACCATCAGCTGGCGCCAGGGCAGGACATCAGCAAGTAC CTGAATCTGGTATCAGCAGAGCCCGAACGGCCACCGTCAGGCTGATCTAC ACCCAGCCGGCTGCACAGCGCGTGTGCCAGCGTTAACGGCGCTCGGC ACCGACTACAGCCTGACCATCTCAACCTGGAACAGGAAGATACTGCCAC TTTTGGCAGCAGGGCAACACACTGGCTTACACCTTGGCGGGCAACAAAGCTG GAAATCACGGCCAGCAGCCTCCGGCAGCGGAAGCCTGGCAGCGCGAGGGCAGC ACCAAGGGCGAGGTGAAGCTGCGAGGAAAGCGGCCCTGGCTGGCCCC CAGAGCTGAGCGTGTACCTGCACCGTGTGAGCCTGAGCCTGCCCCACTAC GTGAGCTGGATCAGGGCCAGGGCTGGAAATGGCTGGCGTGTGATC TGGGGCAGCAGACCACTACTACACAGCCCTGAAGACCCGGCTGACCATC ATCAAGGACAACAGCAAGGCCAGGTGTCTCTGAAGATGAACAGCCTGAGC GACGACACGCCATCTACTACTGCGCCAAGCCTACTACTACAGCGCGAGCTAC GCCATTGGACTACTGGGGCAGGGCACAGCTGTACACAGGCTGAACCTGG TACGGGACCCCTGGCCCTTGTGCTTGTCTGGGTCTGGTGGTGGTGG GGCGTGTGGCTGTCTACAGCCTGCTGTGACCGCTGGCTTACATCATCT GTGAAACGGGGCAGAAAGAAACTCTGTATATATTCAACAAACCATTTTGAGA CCAGTACAAACTACTACAGAGGAAGATGGCTGTAGCTCCGATTTCCAGAAGAA GAAGAAGGGAGATGTGAACTCGGGTGAAAGTTACAGCAGAAGCGCCGAG GCCCTACAGCAGGGCCAGAATCAGCTGTACACAGGCTGAACCTGGCAGAAGG GAAGAGTACGACGCTCTGGATAAGCGGAGAGGCCGGACCTGAGATGGCG AAGCTCGGGAGAAGAACCCCCAGGAAGGGCTGTATAACGAACTGCAGAAAGAC AAGATGGCCAGGGCTGTATCAGGGCTGTACAGCGAGATCAGCAGGCGAG AAGGGCCACGACGGCCCTGTATCAGGGCTGTACAGCGAGGCC GACGCCCTGCACATGCAGGCCCTGCCCGAAGG

TABLE 2-continued

Amino acid sequences of exemplary anti-CD19 molecules		
SEQ ID NO	Region	Sequence
		GAGCACACCGCCATCTACTACTGCGCAACGACTACTACTACGGCGCAGCTACGCCATGGACTACTGGGCCAGGGCACCGTGACGAGC
395	CAR B- CD19 scFv amino acid sequence; with leader	MLLLVTSLLLCELPHPAFLLIPDIQMQTQTTSSLSASLGDRV TISCRASQDISKYLNWYQQKPDGTVKLLIYHTSRL LNWYQQKPDGTVKLLIYHTSRLHSGVPSRFSGS GTDYSLTISNLQEQEDIATYFCQ QGNTLPYTFGGGT KLEITG FCQ QGNTLPYTFGGGT KLEITG STSGSGPKGS GEGSTKGEV K LQESGP GLVAPS QLSVTCTVSGVSLPDYGVSWIRQPPRKGLEWLGVIWGSETTYYNSALKSR LT IKD NSKSQVFLKMNSL QTDDTAI YYCAKHY YGGSYAMD YWGQGTSVTVSS
396	CAR B- full nucleotide sequence; no leader	GACATCCAGATGACCCAGACCCACCTCCAGCCTGAGGCCAGCCTGGGCACCGGG GTGACCATCAGCTGCCGGCAGCCAGCACGCTGATCTACCCACACCCAGCCGCTG CAGCAGAACGGCCAGCGCACCGTCAAGCTGCTGATCTACCCACACCCAGCCGCTG CACAGCGCCGGTAGCCAGGGTTAGCGCAGCCGGCTCCGGCACCGACTACAGC CTGACCATCTCCAACCTGGAACAGAAAGATATCGCACCTACTTTGCCAGCAG GGCAACACACTGCCCTACACCTTGGCGCGGAACAAAGCTGGAAATCACCGGC AGCACCTCCGGCAGCGCCAGCCCTGGCAGGGCAGGGCAGCACCGCC GTGAAAGCTG CAGGGAGCGCCCTGGCCTGGGCTGGCCAGAGCCTGAGC GTGACCTG CAGGGTAGCCAGGGCTGAGCCTGCCC GACTACGGCGT GAGC CTGATC CGGCAGCCCCCAGGAAGGGCTGGAATGGCTGGCGT GATCTGGGCAGCGAG ACCACCTACTAACACAGCGCCCTGAAGAGCGCCGCTGACCATCATCAAGGACAAC AGCAAGAGCAGGTGTTCTGAAGAGTAA CAGCCCTGAGCAGCACCGCC ATCTACTACTG CAGGGACTACTACTACCGCCAGCTGAGCAGCACCGCC TGGGGCAGGGCACCAGCGT GAGCCTGAGCAGCGAATCTAAGTACGGACCGCC T GCCCCCTTGCCTATGTTCTGGGTCTGGTGGTGGTGGTGGTGGC TGCTACAGCTGCTGGTCACCGTGGCCTTCATCATCTTTGGGTGAAACAGGGC AGAAAAGAAACTCTGTATATATTCAACACATTATAGAGACAGTACAAACT ACTCAAGAGGAAGATGGCTGAGCTGCGATTCCAGAAGAAGAAGAAGGAGGA TGTGAAGCTGCGGGTGAGGTT CAGCAGAGCGCCGAGCCCTGCTTACAGCAG GGCAGAATCAGCTGTAACACAGGCTGAAACCTGGCAGAGGGAGAGTACGAC GTCCTGGATAAGCGGAGAGGCCGGACCCCTGAGATGGCGGCAAGCCTGGCG AAGAACCCCCAGGAAGGGCTGTATAACGACTG CAGAAAGACAAGATGGCGAG GCCTACAGCGAGATCGG CATGAAGGGCAGCGGAGGCCGGCAAGGCCACGAC GCCCTG TATCAGGGCTGTCCACCGCCACCAAGGATA CCTACGACGCCCTGCAC ATGCGAGGCCCTGCCCTGAGG 397
397	CAR B- full amino acid transgene sequence; no leader	DIQMTQTSSLSASLGDRV TISCRASQDISKYLNWYQQKPDGTVKLLIYHTSRL HSGVPSRFSGS GS GTDYSLTISNLQEQEDIATYFCQ QGNTLPYTFGGGT KLEITG STSGSGPKGS GEGSTKGEV K LQESGP GLVAPS QSL SVTCTVSGVSLPDYGVSWI RQPPRKGLEWLGVIWGSETTYYNSALKSR LTII KDN SKS QVFLKMNSL QTDDTA IYYCAKHY YGGSYAMD YWGQGTSVTVSS ESKYGP PPCPMFWVLVVGGVLA CYSLRVTFVAFI IFWVTKRGRKLLYIFKQPFMRPVQTTQEEEDGCS CRFP EEEEGG CEL RVKF SRSADAPAYQQQNQLYNELNLRREFYDVL K RGRDPEMGGKPR KNPQEGLYNELQDKMAEAYSEIGMKGERRRGKHDGLYQGLSTATKD TYDALH MQALPPR
398	CAR B- CD19 scFv sequence; no leader	GACATCCAGATGACCCAGACCCACCTCCAGCCTGAGGCCAGCCTGGGCACCG GTGACCATCAGCTGCCGGCAGCCAGCACGCTGATCTACCCACACCCAGCCGCTG CAGCAGAACGGCCAGCGCACCGTCAAGCTGCTGATCTACCCACACCCAGCCGCTG CACAGCGCCGGTAGCCAGGGTTAGCGCAGCCGGACTACGGCGCAGCCACTACAGC CTGACCATCTCCAACCTGGAACAGAAAGATATCGCACCTACTTTGCCAGCAG GGCAACACACTGCCCTACACCTTGGCGCGGAACAAAGCTGGAAATCACCGGC AGCACCTCCGGCAGCGCCAGCCCTGGCAGCGCCGAGGGCAGCACCAAGGGCAG GTGAAGCTG CAGGGAAAGCGCCCTGGCCTGGTGGCAGGCCAGCCAGGCC GTGACCTG CAGGGTAGCCAGGGCTGAGCCTGCCC GACTACGGCGT GAGC CTGATC CGGCAGCCCCCAGGAAGGGCTGGAATGGCTGGCGT GATCTGGGCAGCGAG ACCACCTACTAACACAGCGCCCTGAAGAGCGCCGCTGACCATCATCAAGGACAAC AGCAAGAGCAGGTGTTCTGAAGATGAACAGCGCTGAGCAGCACCGACGACACCGCC ATCTACTACTG CAGGGACTACTACTACCGCCAGCTGAGCAGCTACGGCATGGACTAC TGGGGCAGGGCACCAGCGT GACCGCAG 399
399	CAR B- CD19 scFv sequence; no leader	DIQMTQTSSLSASLGDRV TISCRASQDISKYLNWYQQKPDGTVKLLIYHTSRL HSGVPSRFSGS GS GTDYSLTISNLQEQEDIATYFCQ QGNTLPYTFGGGT KLEITG STSGSGPKGS GEGSTKGEV K LQESGP GLVAPS QSL SVTCTVSGVSLPDYGVSWI RQPPRKGLEWLGVIWGSETTYYNSALKSR LTII KDN SKS QVFLKMNSL QTDDTA IYYCAKHY YGGSYAMD YWGQGTSVTVSS

## BCMA CAR

In some embodiments, the CAR-expressing cell described herein is a BCMA CAR-expressing cell (for example, a cell expressing a CAR that binds to human BCMA). Exemplary BCMA CARs can include sequences disclosed in Table 1 or 16 of WO2016/014565, incorporated herein by reference. The BCMA CAR construct can include an optional leader

<sup>60</sup> sequence; an optional hinge domain, for example, a CD8 hinge domain; a transmembrane domain, for example, a CD8 transmembrane domain; an intracellular domain, for example, a 4-1BB intracellular domain; and a functional signaling domain, for example, a CD3 zeta domain. In certain embodiments, the domains are contiguous and in the same reading frame to form a single fusion protein. In other

embodiments, the domains are in separate polypeptides, for example, as in an RCAR molecule as described herein.

In some embodiments, the BCMA CAR molecule includes one or more CDRs, VH, VL, scFv, or full-length sequences of BCMA-1, BCMA-2, BCMA-3, BCMA-4, BCMA-5, BCMA-6, BCMA-7, BCMA-8, BCMA-9, BCMA-10, BCMA-11, BCMA-12, BCMA-13, BCMA-14, BCMA-15, 149362, 149363, 149364, 149365, 149366, 149367, 149368, 149369, BCMA\_EBB-C1978-A4, BCMA\_EBB-C1978-G1, BCMA\_EBB-C1979-C1, BCMA\_EBB-C1978-C7, BCMA\_EBB-C1978-D10, BCMA\_EBB-C1979-C12, BCMA\_EBB-C1980-G4, BCMA\_EBB-C1980-D2, BCMA\_EBB-C1978-A10, BCMA\_EBB-C1978-D4, BCMA\_EBB-C1980-A2, BCMA\_EBB-C1981-C3, BCMA\_EBB-C1978-G4, A7D12.2, C11D5.3, C12A3.2, or C13F12.1 disclosed in WO2016/014565, or a sequence substantially (for example, 95-99%) identical thereto.

Additional exemplary BCMA-targeting sequences that can be used in the anti-BCMA CAR constructs are disclosed in WO 2017/021450, WO 2017/011804, WO 2017/025038, WO 2016/090327, WO 2016/130598, WO 2016/210293, WO 2016/090320, WO 2016/014789, WO 2016/094304, WO 2016/154055, WO 2015/166073, WO 2015/188119, WO 2015/158671, U.S. Pat. Nos. 9,243,058, 8,920,776, 9,273,141, 7,083,785, 9,034,324, US 2007/0049735, US 2015/0284467, US 2015/0051266, US 2015/0344844, US 2016/0131655, US 2016/0297884, US 2016/0297885, US 2017/0051308, US 2017/0051252, US 2017/0051252, WO 2016/020332, WO 2016/087531, WO 2016/079177, WO 2015/172800, WO 2017/008169, U.S. Pat. No. 9,340,621, US 2013/0273055, US 2016/0176973, US 2015/0368351, US 2017/0051068, US 2016/0368988, and US 2015/0232557, herein incorporated by reference in their entirety. In some embodiments, additional exemplary BCMA CAR constructs are generated using the VH and VL sequences from PCT Publication WO2012/0163805 (the contents of which are hereby incorporated by reference in its entirety).

In some embodiments, BCMA CARs comprise a sequence, for example, a CDR, VH, VL, scFv, or full-CAR sequence, disclosed in Tables 3-15, or a sequence having at least 80%, 85%, 90%, 95%, or 99% identity thereto. In some embodiments, the antigen binding domain comprises a human antibody or a human antibody fragment. In some embodiments, the human anti-BCMA binding domain comprises one or more (for example, all three) LC CDR1, LC CDR2, and LC CDR3 of a human anti-BCMA binding domain described herein (for example, in Tables 3-15), and/or one or more (for example, all three) HC CDR1, HC CDR2, and HC CDR3 of a human anti-BCMA binding domain described herein (for example, in Tables 3-15). In some embodiments, the human anti-BCMA binding domain comprises a human VL described herein (for example, in Tables 3, 7, 11, 11a, and 12) and/or a human VH described herein (for example, in Tables 3, 7, 11, 11a, and 12). In some embodiments, the anti-BCMA binding domain is a scFv comprising a VL and a VH of an amino acid sequence of Tables 3, 7, 11, 11a, and 12. In some embodiments, the anti-BCMA binding domain (for example, an scFv) comprises: a VL comprising an amino acid sequence having at least one, two or three modifications (for example, substitutions, for example, conservative substitutions) but not more than 30, 20 or 10 modifications (for example, substitutions, for example, conservative substitutions) of an amino acid sequence provided in Tables 3, 7, 11, 11a, and 12, or a sequence with 95-99% identity with an amino acid sequence of Tables 3, 7, 11, 11a, and 12, and/or a VH comprising an amino acid sequence having at least one, two or three modifications (for example, substitutions, for example, conservative substitutions) but not more than 30, 20 or 10 modifications (for example, substitutions, for example, conservative substitutions) of an amino acid sequence provided in Tables 3, 7, 11, 11a, and 12, or a sequence with 95-99% identity to an amino acid sequence of Tables 3, 7, 11, 11a, and 12.

TABLE 3

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Amino acid and nucleic acid sequences of exemplary PALLAS-derived anti-BCMA molecules

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SEQ ID NO	Name/ Description	Sequence
<u>R1B6</u>		
SEQ ID NO: 44	HCDR1 (Kabat)	SYAMS
SEQ ID NO: 45	HCDR2 (Kabat)	AISGSGGSTYYADSVKG
SEQ ID NO: 46	HCDR3 (Kabat)	REWVPYDVSWYPDY
SEQ ID NO: 47	HCDR1 (Chothia)	GFTFSSY
SEQ ID NO: 48	HCDR2 (Chothia)	SGSGGS
SEQ ID NO: 46	HCDR3 (Chothia)	REWVPYDVSWYPDY
SEQ ID NO: 49	HCDR1 (IMGT)	GFTFSSYA
SEQ ID NO: 50	HCDR2 (IMGT)	ISGSGGST

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TABLE 3-continued

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Amino acid and nucleic acid sequences of exemplary PALLAS-derived anti-BCMA molecules

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SEQ ID NO	Name/Description	Sequence
SEQ ID NO: 51	HCDR3 (IMGT)	ARREWVPYDVSWYFDY
SEQ ID NO: 52	VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKLEWVS AISGSGGSTYYADSVKGRFTISRDNNSKNTLYLQMNSLRAEDTAVYYCARR EWPYDVSWYFDYWGQGTLVTVSS
SEQ ID NO: 53	DNA VH	GAAGTGCAGTTGCTGGAGTCAGCGGGAGGACTGGTGCAGCCGGAGG ATCGCTTCGCTTGAGCTGCGCAGCCTCAGGCTTACCTTCCTCCCTAC GCCATGTCCTGGGTCAAGACAGGCTCCCGGAAGGGACTGGAATGGGT GTCGGCATTAGCGGTTCCGGCGGAAGCACTTACTATGCCGACTCTGT GAAGGGCCCTTCACTATCTCCGGGACAACCTCAAGAACACCCCTGTA TCTCCAATGAATTCCCTGAGGGCGAAGATAACCGCGGTGTACTACTG CGCTAGACGGGAGTGGGTGCCCTACGATGTCAGCTGGTACTTCGACTA CTGGGGACAGGGCACTCTCGTACTGTGCTCC
SEQ ID NO: 54	LCDR1 (Kabat)	RASQSISSYLN
SEQ ID NO: 55	LCDR2 (Kabat)	AASSLQS
SEQ ID NO: 56	LCDR3 (Kabat)	QQSYSTPLT
SEQ ID NO: 57	LCDR1 (Chothia)	SQSISSY
SEQ ID NO: 58	LCDR2 (Chothia)	AAS
SEQ ID NO: 59	LCDR3 (Chothia)	SYSTPL
SEQ ID NO: 60	LCDR1 (IMGT)	QSISYY
SEQ ID NO: 61	LCDR2 (IMGT)	AAS
SEQ ID NO: 62	LCDR3 (IMGT)	QQSYSTPLT
SEQ ID NO: 63	VL	DIQMTQSPSSLSASVGDRVITICRASQSISSYLNWYQQKPGKAPKLLIYAA SSLQSGVPSRSFGSGSGTDFTLTISLQPEDFATYYCQQSYSTPLTFGQGTK VEIK
SEQ ID NO: 64	DNA VL	GACATTCAATGACTCAGTCCCCGTCTCCCTCTCCGCCTCCGTGGGA GATCGCGTCACGATCACGTGCAGGGCAGCCAGACATCTCCAGCTAC CTGAACTGGTACCAAGCAGAAGCCAGGGAAAGGCACCGAAGCTCCTGAT CTACGGCGTAGCTCGCTGAGCTCCGGCGTCCCTCACGGTTCTCGGG ATCGGGCTCAGGCACCACTTCACCCCTGACCATTTAGCAGCCTGCAGCC GGAGGACTTCGCGACATACTACTGTGAGCAGTCATACTCCACCCCTCT GACCTTCGGCCAAGGGACCAAAGTGGAGATCAAG
SEQ ID NO: 65	Linker	GGGGSGGGGGGGGGGGGGGG
SEQ ID NO: 66	scFv (VH-linker-VL)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKLEWVS AISGSGGSTYYADSVKGRFTISRDNNSKNTLYLQMNSLRAEDTAVYYCARR EWPYDVSWYFDYWGQGTLVTVSSGGGGGGGGGGGGGGGGSDIQ MTQSPSSLSASVGDRVITICRASQSISSYLNWYQQKPGKAPKLLIYAASSL QSGVPSRSFGSGSGTDFTLTISLQPEDFATYYCQQSYSTPLTFGQGTKVEIK
SEQ ID NO: 67	DNA scFv	GAAGTGCAGTTGCTGGAGTCAGCGGGAGGACTGGTGCAGCCGGAGG ATCGCTTCGCTTGAGCTGCGCAGCCTCAGGCTTACCTTCCTCCCTAC GCCATGTCCTGGGTCAAGACAGGCTCCCGGAAGGGACTGGAATGGGT GTCGGCATTAGCGGTTCCGGCGGAAGCACTTACTATGCCGACTCTGT GAAGGGCCCTTCACTATCTCCGGGACAACCTCAAGAACACCCCTGTA TCTCCAATGAATTCCCTGAGGGCGAAGATAACCGCGGTGTACTACTG CGCTAGACGGGAGTGGGTGCCCTACGATGTCAGCTGGTACTTCGACTA CTGGGGACAGGGCACTCTCGTACTGTGACTGTGCTCCGGTGGTGGGATC GGGGGGTGGTGGTGGGGCGGAGGAGATCTGGAGGAGGAGGTGG

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TABLE 3-continued

Amino acid and nucleic acid sequences of exemplary PALLAS-derived anti-BCMA molecules

SEQ NO	ID	Name/ Description	Sequence
			ACATTCAAATGACTCAGTCCCCGTCCCTCCCTCTCCGCCCTCGTGGAG ATCGCGCACGATCACGTGCAGGGCAGCCAGAGCATCTCAGCTACC TGAACTGGTACCGACAGAAGCCAGGGAGGCACCGAACGCTCTGATC TACGCCGCTAGCTCGCTCAGTCGGCGTCCCTCACGGTTCTCGGGA TCGGGCTCAGGGACCTTCACCTCACGGTGGGACTTACCGACCTGAGC GAGGACTTCGCGACATACTACTGTCAGCAGTCAGCTGTACTACTG LYQGLSTATKDTYDALHMQALP GAAGTCAGTTGCTGGAGTCAGCCGGAGGACTGGTGCAGCCCCGGAGG ATCGCTTCCGCTTGAGCTCGCGCAGCCTCAGGGCTTACCTTCTCTCTAC GCCATGTCTGGGTCAAGCAGGCTCCCGGAAGGGACTGGAATGGGT GTCCGCGATTAGCGGTTCCGGCGGAAGCAGCTACTATGCCGACTCTGT GAAGGCCGCTTCACTATCTCCGGGACAACCTCAAGAACACCCCTGA TCTCCAATGAATTCCCTGAGGGCCGAAGATAACGCCGTGTACTACTG CGCTAGACGGGAGTGGGTGCCCTACGATGTCAGCTGTACTTCGACTA CTGGGGACAGGGCACTCTCGTACTGTGTACTCTCGGGTGGTGGATC GGGGGGTGGTGGTTCGGGCGAGGAGGATCTGGAGGAGGAGGGTCCG
NO: 66	Full CAR amino acid sequence		EVQLLESGGGLVQPFGSRLSCAASGFTFSSYAMSWVRQAPKGLEWVS AISGSGGSTYYADSVKGRFTISRDNNSKNTLYLQMNSLRAEDTAVYYCARR MTQSPSLLASAVGDRVITCRASQSISYLNWYQQPKGKAPLIIYAASSL QSGVPSPRSGSGSTDFLTISLQPEDFATYYCQQSYSTPLTEFGQGTKEI KTTTPAPRPPTPAPTIAQPLSLRPEACRPAAGGAVHTRGLFACDIYIWAP LAGTCGVLLSLLVITYLCKRGRKKLLYIFKQPFMRPVQTTQEEEDGCSRFP EEEEGGCERLVRKPSRSADAPAYQGQNLQYNELNLRGEEYDVLDRKRG RDPEMGGKPRRNPKQEGLYNELQDKDMAEAYSEIGMKGERRRKGHDG LYQGLSTATKDTYDALHMQALP GAAGTCAGTTGCTGGAGTCAGCCGGAGGACTGGTGCAGCCCCGGAGG ATCGCTTCCGCTTGAGCTCGCGCAGCCTCAGGGCTTACCTTCTCTCTAC GCCATGTCTGGGTCAAGCAGGCTCCCGGAAGGGACTGGAATGGGT GTCCGCGATTAGCGGTTCCGGCGGAAGCAGCTACTATGCCGACTCTGT GAAGGCCGCTTCACTATCTCCGGGACAACCTCAAGAACACCCCTGA TCTCCAATGAATTCCCTGAGGGCCGAAGATAACGCCGTGTACTACTG CGCTAGACGGGAGTGGGTGCCCTACGATGTCAGCTGTACTTCGACTA CTGGGGACAGGGCACTCTCGTACTGTGTACTGTGTACTCTCGGGTGGATC GGGGGGTGGTGGTTCGGGCGAGGAGGATCTGGAGGAGGAGGGTCCG
NO: 67	Full CAR DNA sequence		ACATTCAAATGACTCAGTCCCCGTCCCTCCCTCTCCGCCCTCGTGGAG ATCGCGCACGATCACGTGCAGGGCAGCCAGAGCATCTCAGCTACC TGAACTGGTACCGACAGAAGCCAGGGAGGCACCGAACGCTCTGATC TACGCCGCTAGCTCGCTCAGTCGGCGTCCCTCACGGTTCTCGGGA TCGGGCTCAGGCCAGCAGCTTACCCCTGACCTAGCAGCTGCAGCCG GAGGACTTCGCGACATACTACTGTCAGCAGTCATACTCCACCCCTGT ACCTTCGGCCAAGGGACAAAGTGGAGATCAAGACCAACTACCCAGC ACCGAGGCCACCCACCCGGCTCTACCATCGCTCCAGCCCTGTG CCTCGCTCCGGAGGCATGTAACCGCAGCTGGTGGGGCCGTGACATAC CCGGGGCTTGAACCTCGCTCGGATATCTACATTTGGGCCCCCTGGCT GGTACTTCGCGGGTCTCGCTGCTGTTCACTCGTGTACTCTTACTGTA AGCCGGTGGAAAGCTGCTGTAACATCTTAAGCAACCCCTCATGA GGCCTGTGAGACTACTCAAGAGGAGGACGGCTGTTCATGCCGGTCC CAGAGGAGGAGGAAGGCCGCTCGGAACCTGCCGCTGAAATTAGCCGC AGCCGAGATGCTCCAGCCTACCCAGCAGGGCAGAACCCAGCTTACAA CGAACTCAATCTGGTCGGAGAGAGGAGTACGACGTGCTGACAAGC GGAGAGGAGGCCAGAAATGGCGGGAGCCGCGCAGAAAGAA TCCCAAGAGGGCTGTACAACGAGCTCCAAAGGATAAGATGGCAG AAGCTATAGCGAGATTGGTATGAAAGGGGAACGCAGAACAGGCAA GGCCACGCGACTGTACCGGGACTCAGCACCGCCACCAAGGACAC CTATGACGCTCTTCACATGCAAGGCCCTGCCCTCGG
	R1F2		
NO: 44	SEQ ID HCDR1 (Kabat)	SYAMS	
NO: 45	SEQ ID HCDR2 (Kabat)	AISGSGGSTYYADSVKG	
NO: 68	SEQ ID HCDR3 (Kabat)	REWWYDDWYLDY	
NO: 47	SEQ ID HCDR1 (Chothia)	GFTFSSY	
NO: 48	SEQ ID HCDR2 (Chothia)	SGSGGS	
NO: 68	SEQ ID HCDR3 (Chothia)	REWWYDDWYLDY	
NO: 49	SEQ ID HCDR1 (IMGT)	GFTFSSYA	

TABLE 3-continued

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Amino acid and nucleic acid sequences of exemplary PALLAS-derived anti-BCMA molecules

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SEQ NO	ID	Name/ Description	Sequence
SEQ NO: 50	HCDR2 (IMGT)	ISGGGGT	
SEQ NO: 69	HCDR3 (IMGT)	ARREWWYDDWYLDY	
SEQ NO: 70	VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKLEWVS AISGGGGTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARR EWWYDDWYLDYWGQGTLVTVSS	
SEQ NO: 71	DNA VH	GAAGTCAGTTGCTGGAGTCAGCGGGAGGACTGGTGCAGCCGGAGG ATCGCTTCGCTTGAGCTGCGCAGCCTCAGGCTTACCTTCTCTCTAC GCCATGTCCTGGGTCAAGACAGGCTCCCGGAAGGGACTGGAATGGGT GTCGGCATTAGCGGTTCCGGCGGAAGCAGCTACTATGCCACTCTGT GAAGGGCCGCTTCACTATCTCCGGGACAACCTCCAAGAACACCCCTGTA TCTCCAAATGAATTCCCTGAGGGCCGAAGATAACCGCGGTGTACTACTG CGCTAGACGGGAGTGGTGTACGACGATTGGTACCTGGACTACTGGG GACAGGGCACTCTCGTACTGTGTCCTCC	
SEQ NO: 54	LCDR1 (Kabat)	RASQSISSYLN	
SEQ NO: 55	LCDR2 (Kabat)	AASSLQS	
SEQ NO: 56	LCDR3 (Kabat)	QQSYSTPLT	
SEQ NO: 57	LCDR1 (Chothia)	SQSISYY	
SEQ NO: 58	LCDR2 (Chothia)	AAS	
SEQ NO: 59	LCDR3 (Chothia)	SYSTPL	
SEQ NO: 60	LCDR1 (IMGT)	QSISYY	
SEQ NO: 58	LCDR2 (IMGT)	AAS	
SEQ NO: 56	LCDR3 (IMGT)	QQSYSTPLT	
SEQ NO: 61	VL	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAA SSLQSGVPSRFSGSGSTDFTLTISSLQPEDFATYYCQQSYSTPLTFQGQTK VEIK	
SEQ NO: 62	DNA VL	GACATTCAAATGACTCAGTCCCCTCTCCCTCTCCGCTCCGTGGGA GATCGCGTCACGATCACGTGCAGGGCCAGCAGAGCATCTCCAGCTAC CTGAACTGGTACAGCAGAAGCAGGAAGGACCCGAAAGCTCTGT CTACGCGCTAGTCGCTGCAGTCGGCTCCCTCACGGTCTCGG ATCGGGCTCAGGACCCGACTTCACCTTGACCATTAGCAGCTGCAGCC GGAGGACTTCGGACATACTACTGTCAAGCTCATACTCCACCCCTCT GACCTTCGGCCAAGGGACCAAGTGGAGATCAAG	
SEQ NO: 63	Linker	GGGGSGGGGGGGGGGGGGGG	
SEQ NO: 72	scFv (VH-linker-VL)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKLEWVS AISGGGGTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARR EWWYDDWYLDYWGQGTLVTVSSGGGGSGGGGGGGGGGGGGGGSDIQM QSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAAASSLQS GVPSRFSGSGSTDFTLTISSLQPEDFATYYCQQSYSTPLTFQGQTKVEIK	
SEQ NO: 73	DNA scFv	GAAGTCAGTTGCTGGAGTCAGCGGGAGGACTGGTGCAGCCGGAGG ATCGCTTCGCTTGAGCTGCGCAGCCTCAGGCTTACCTTCTCTCTAC GCCATGTCCTGGGTCAAGACAGGCTCCCGGAAGGGACTGGAATGGGT GTCGGCATTAGCGGTTCCGGCGGAAGCAGCTACTATGCCACTCTGT GAAGGGCCGCTTCACTATCTCCGGGACAACCTCCAAGAACACCCCTGTA TCTCCAAATGAATTCCCTGAGGGCCGAAGATAACCGCGGTGTACTACTG CGCTAGACGGGAGTGGTGTACGACGATTGGTACCTGGACTACTGGG	

TABLE 3-continued

Amino acid and nucleic acid sequences of exemplary PALLAS-derived anti-BCMA molecules			
SEQ ID NO	Name/Description	Sequence	
		GACAGGGCACTCTCGTGAETGTCTCCGGTGGTGGATCGGGG GTGTTGGTTCGGGGAGGAGGACTCGAGGGAGGAGGATCGCATT CAAATGACTCAGTCCCCGCTCCCTCTCCGCCCTCGGGAGATCGC GTACAGCATCACGTCAAGGGCAGCCAGAACATCTCCACGCTAC TGTTACCAGCAGAAGCCAGGGAAAGGCACCGAAGCTCTGATCTAC CGCTAGCTCGCAGTCGGGTCCTCCACGGTTCTGGGATCGGG CTCAGGCACCGACTTCACCCCTGACCATTAAGCAGCCTGAGCGGAGGA CTTCGGCACATACTACTGTAGCAGCTACACTCCACCCCTCGACCTTC GGCCAAGGGACCAAGTGGAGATCAAGAACACTACCCAGCAGGAG EVQLLESGLVQPQGSLRLSCAASGFTFSSYAMSWVRQAPGKLEWVS AISGSGGSTYYADSVKGRFTIQRDNNSKNTLYLQMNSLRAEDTAVYVCCR EWYWDWYLDYWQGQTLTVTSSGGGGGGGGGGGGGGGGSDIQMT QSPSSLASAVGDRVTITCRASOSISSYLNWYQQPKPDKAPKLIIYAASSLQS GVPSRFSGSGSGTDFTLTISLSPDFTAYYQQSYSTPLTFQGQTKVEIKT TTPAAPRPTPAPTIASQPLSLRPEACRPAAGGAVHTRQLDFACDIYIWAPLA GTCGVLLSLVITYCKRGRKKLLYIFKQPFMRPVQTQEEDGCSCRFPEE EEGGCELRVFKFSRSADAPAYQQGNQNLNELNLGRREEYDVLDKRRGR DPEMGGKPRRKKNPQEGLYNELQKDJKMAEAYSEIGMKGERRRKGKGDGL YQGLSTATKDTYDALHMQLPPR	
SEQ ID NO: 74	Full CAR amino acid sequence	GAAGTGCAGTTGCTGGAGTCAGGGGGAGGACTGGTGCAGCCGGAGG ATCGCTTCGCTGGAGTCGCAGCCTCAGGCTTACCTCTCCTAC GCCATGTCCTGGGTCAAGCAGGGCTCCGGGAAGGGACTGGAATGGGT GTCCGCCATTAGCGGTTCCGGCGGAAGCACTTACTATGCCGACTCTGT GAAGGGCCGCTTCACTATCTCCGGGAACACTCCAAGAACACCCCTGT TCTCCAAATGAATTCCCTGAGGGCCGAAGATACCGCGGTGACTACTG CGCTAGACGGGAGTGGTGGTACGACGATGGTACCTGGACTACTGG GACAGGGCACTCTCGTGAETGTCTCCGGTGGTGGGATCGGGG GTGGTGGTTCGGGGAGGAGGAGCTCGAGGGAGGAGGGATCGCATT CAAATGACTCAGTCCCCCTCCCTCTCGGCTCCGGGAGATCGC GTACAGCATCACGTCAAGGGCAGCCAGAACATCTCCAGCTAC TGGTACACAGCAGAACGGAGGGCAGCGAACGACTCTGATCTAC CGCTAGCTCGCTGAGTCGGGCTCCCTCACGGTTCTGGGATCGGG CTCAGGCACCGACTTCACCCCTGACCATTAAGCAGCCTGAGCGGAGGA CTTCGGCACATACTACTGTAGCAGCTACACTCCACCCCTCTGACCTC GGCCAAGGGACCAAGTGGAGATCAAGAACACTACCCAGCAGGAG GCCACCCACCCCGCTCTACCATCGCTCCCGCTGTCCCTCGCT CCGGAGGAGTGAACCGCAGCTGGTGGGGCGTGCATACCCGGGG TCTTGACTTCGCTCGATATCTACATTGGGCCCCTGGCTGGTACT TGCGGGTCTGCTGTTCACTCGTGTACACTTTACTGTAAGCGCG GTCGGAAGAGCTGCTGTACATTTAAGCAACCCCTCATGAGGCTG TGCAGACTACTCAAGAGGAGGACGGCTGTTCACTGCCGTTCCAGAGG AGGAGGAAGGGCGGCTGCGAACACTGCGCTGAAATTCAAGCGCAGCGCA GATCTCCAGCCTACACAGCAGGGCAGAACAGCTACAACGAACT CAATCTGGTCGGAGAGAGGAGTACGACGTGCTGGACAAGCGGAGAG GACGGGACCCAGAATGGCGGGAGGCCCGCAGAAAAGATCCCAA GAGGGCCTGTACACAGCTCCAAAAGGATAAGATGGCAGAAGCCTA TAGGGAGATTGGTATGAAAGGGAAACGAGAGAGGAAAGGGCACG ACGGACTGTACCAAGGGACTCAGCACCGGCCACCAAGGACACCTATGAC GCTCTTCACATGCAGGCCCTGCCCTCG	
SEQ ID NO: 75	Full CAR DNA sequence	GAAGTGCAGTTGCTGGAGTCAGGGGGAGGACTGGTGCAGCCGGAGG ATCGCTTCGCTGGAGTCGCAGCCTCAGGCTTACCTCTCCTAC GCCATGTCCTGGGTCAAGCAGGGCTCCGGGAAGGGACTGGAATGGGT GTCCGCCATTAGCGGTTCCGGCGGAAGCACTTACTATGCCGACTCTGT GAAGGGCCGCTTCACTATCTCCGGGAACACTCCAAGAACACCCCTGT TCTCCAAATGAATTCCCTGAGGGCCGAAGATACCGCGGTGACTACTG CGCTAGACGGGAGTGGTGGTACGACGATGGTACCTGGACTACTGG GACAGGGCACTCTCGTGAETGTCTCCGGTGGTGGGATCGGGG GTGGTGGTTCGGGGAGGAGGAGCTCGAGGGAGGAGGGATCGCATT CAAATGACTCAGTCCCCCTCCCTCTCGGCTCCGGGAGATCGC GTACAGCATCACGTCAAGGGCAGCCAGAACATCTCCAGCTAC TGGTACACAGCAGAACGGAGGGCAGCGAACGACTCTGATCTAC CGCTAGCTCGCTGAGTCGGGCTCCCTCACGGTTCTGGGATCGGG CTCAGGCACCGACTTCACCCCTGACCATTAAGCAGCCTGAGCGGAGGA CTTCGGCACATACTACTGTAGCAGCTACACTCCACCCCTCTGACCTC GGCCAAGGGACCAAGTGGAGATCAAGAACACTACCCAGCAGGAG GCCACCCACCCCGCTCTACCATCGCTCCCGCTGTCCCTCGCT CCGGAGGAGTGAACCGCAGCTGGTGGGGCGTGCATACCCGGGG TCTTGACTTCGCTCGATATCTACATTGGGCCCCTGGCTGGTACT TGCGGGTCTGCTGTTCACTCGTGTACACTTTACTGTAAGCGCG GTCGGAAGAGCTGCTGTACATTTAAGCAACCCCTCATGAGGCTG TGCAGACTACTCAAGAGGAGGACGGCTGTTCACTGCCGTTCCAGAGG AGGAGGAAGGGCGGCTGCGAACACTGCGCTGAAATTCAAGCGCAGCGCA GATCTCCAGCCTACACAGCAGGGCAGAACAGCTACAACGAACT CAATCTGGTCGGAGAGAGGAGTACGACGTGCTGGACAAGCGGAGAG GACGGGACCCAGAATGGCGGGAGGCCCGCAGAAAAGATCCCAA GAGGGCCTGTACACAGCTCCAAAAGGATAAGATGGCAGAAGCCTA TAGGGAGATTGGTATGAAAGGGAAACGAGAGAGGAAAGGGCACG ACGGACTGTACCAAGGGACTCAGCACCGGCCACCAAGGACACCTATGAC GCTCTTCACATGCAGGCCCTGCCCTCG	
<u>R1G5</u>			
SEQ ID NO: 44	HCDR1 (Kabat)	SYAMS	
SEQ ID NO: 45	HCDR2 (Kabat)	AISGSGGSTYYADSVVK	
SEQ ID NO: 76	HCDR3 (Kabat)	REWWGESWLFDY	
SEQ ID NO: 47	HCDR1 (Chothia)	GFTFSSY	
SEQ ID NO: 48	HCDR2 (Chothia)	SGSGGS	
SEQ ID NO: 76	HCDR3 (Chothia)	REWWGESWLFDY	
SEQ ID NO: 49	HCDR1 (IMGT)	GFTFSSY	

TABLE 3-continued

Amino acid and nucleic acid sequences of exemplary PALLAS-derived anti-BCMA molecules			
SEQ ID NO	Name/ Description	Sequence	
SEQ ID NO: 50	HCDR2 (IMGT)	ISGSGGST	
SEQ ID NO: 77	HCDR3 (IMGT)	ARREWWGESWLFDY	
SEQ ID NO: 78	VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKLEWVS AISGSGGTYYADSVKGRFTISRDNNSKNTLYLQMNSLRAEDTAVYYCARR EWWGESWLFDYWQGTLVTVSS	
SEQ ID NO: 79	DNA VH	GAAGTCAGTTGCTGGAGTCAGCGGGAGGACTGGTGCAGCCGGAGG ATCGCTTCGCTTGAGCTGCGCAGCCTCAGGCTTACCTTCTCCTCCTAC GCCATGTCCTGGGTCAAGACAGGCTCCCGGAAGGGACTGGAATGGGT GTCGGCCATTAGCGGTTCCGGCGGAAGCACTTACTATGCCGACTCTGT GAAGGGCCGCTTCACTATCTCCGGGACAACCTCAAGAACACCCCTGTA TCTCCAATGAATTCCCTGAGGGCGAAGATAACCGCGGTGTACTACTG CGCTAGACGGGAGTGGTGGGGAGAAAGCTGGCTGTTGACTACTGGG GACAGGGCACCTCGTACTGTGTCC	
SEQ ID NO: 54	LCDR1 (Kabat)	RASQSISSYLN	
SEQ ID NO: 55	LCDR2 (Kabat)	AASSLQS	
SEQ ID NO: 56	LCDR3 (Kabat)	QQSYSTPLT	
SEQ ID NO: 57	LCDR1 (Chothia)	SQSISSY	
SEQ ID NO: 58	LCDR2 (Chothia)	AAS	
SEQ ID NO: 59	LCDR3 (Chothia)	SYSTPL	
SEQ ID NO: 60	LCDR1 (IMGT)	QSISYY	
SEQ ID NO: 58	LCDR2 (IMGT)	AAS	
SEQ ID NO: 56	LCDR3 (IMGT)	QQSYSTPLT	
SEQ ID NO: 61	VL	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAA SSLQSGVPSPRSFGSGSGTDFLTISLQPEDPATYYCQQSYSTPLTFQGQTK VEIK	
SEQ ID NO: 62	DNA VL	GACATTCAAATGACTCAGTCCCCGTCCCTCCCTCCGCCTCCGTGGGA GATCGCGTCACGATCACGTGCAAGGCCAGCAGAGCATCTCCAGCTAC CTGAACTGGTACCAAGCAGAAGGCCAGGGAAAGGCACCGAAGGCTCTGAT CTACGGCTCAGGCACTTACCCCTGACCATTAGCAGCTGCAGCC GGAGGACTTCGGCACATACTACTGTCAAGCAGTCATACTCCACCCCTCT GACCTTCGGCCAAGGGACAAAGTGGAGATCAAG	
SEQ ID NO: 63	Linker	GGGGSGGGGGGGGGGGGGGS	
SEQ ID NO: 80	scFv (VH-linker-VL)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKLEWVS AISGSGGTYYADSVKGRFTISRDNNSKNTLYLQMNSLRAEDTAVYYCARR EWWGESWLFDYWQGTLVTVSSGGGGGGGGGGGGGGSDIQMT QSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQS GVPSRFSGSGSGTDFLTISLQPEDPATYYCQQSYSTPLTFQGQTKVEIK	
SEQ ID NO: 81	DNA scFv	GAAGTCAGTTGCTGGAGTCAGCGGGAGGACTGGTGCAGCCGGAGG ATCGCTTCGCTTGAGCTGCGCAGCCTCAGGCTTACCTTCTCCTCCTAC GCCATGTCCTGGGTCAAGACAGGCTCCCGGAAGGGACTGGAATGGGT GTCGGCCATTAGCGGTTCCGGCGGAAGCACTTACTATGCCGACTCTGT GAAGGGCCGCTTCACTATCTCCGGGACAACCTCAAGAACACCCCTGTA TCTCCAATGAATTCCCTGAGGGCGAAGATAACCGCGGTGTACTACTG	

TABLE 3-continued

Amino acid and nucleic acid sequences of exemplary PALLAS-derived anti-BCMA molecules			
SEQ ID NO	Name/Description	Sequence	
		CGCTAGACGGGAGTGGGGGAGAAAGCTGGCTTCTGACTACTGGG GACAGGGCACTCTGTGACTGTCTCCGGTGGTGGATCAGGGGG GTGGTGGCTTCGGGGAGGAGATCTGGAGGAGGAGGGCTGGAGATT CAAATGACTCAGTCAGCCCCCTCCTCTCGCTCCGGAGATCGC GTCACGATCACGTGCAGGGCAGCCAGACATCTCCAGCTACCTGAAC TGGTACCAAGCAGAACGGAGGAGGAGCTCTGATCTACGC CGCTAGCTCGTGCAGTCCGGCCTTCACGGTTCTCGGGATCAGGG CTCAGGCAACCGACTTACCCCTGACCATTAGCAGCCTGAGCCGGAGGA CTTCGCGACATACTACTGTCAGCAGTCATACTCCACCCCTGACCTTC GGCCAAGGGACAAAGTGGAGATCAAG	
SEQ ID NO: 82	Full CAR amino acid sequence	EVQLLESGGGLVQPQGSLRLSCAASGFTFSSYAMSWSVRQAPKGLEWWS AISGGGGTYYADSVKGRFTISRDNSKNLTYLQMNSLRAEDTAVYYCARR EWWGESWLFDYWGGTLVTVSSGGGSGGGGSGGGGGSDIQM QSPSSLASAVGDRVTITCRASQSISYYLNWYQQKPGKAPKLLIYAAASSLOS GVPSRFSGSGSTDFDTLTLISLQPFEDPFTTYCQQSYSTPLTFQGQTKVEAPLA TTPAPRPPTPAPIIASQPLSLSRPEACRPAAGGAVHTRGLDFACDIYIWAPLA GTCGVLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEDGCSCRFPEE EEGGCELRRVKFSRADAPAYQQCQNLYNELNLGRREYDVLDRKRRGR DPEMGGKPRRNPKNQEGILYNEQKDKMABAYSEIGMKGERRRKGHDGL YQGLSTATKTDYDALHMQLPPR	
SEQ ID NO: 83	Full CAR DNA sequence	GAAGTGCAGTTGCTGGAGTCAGGGGGAGGACTGGTGCAAGCCGGAGG ATCGCTTCGCTTGGAGCTCGCAGCCTCAGGCTTACCTCTCCCTAC GCCATGTCTGGGTCAGCAGGCTCCCGGAAGGGACTTGAATGGGT GTCCGCCATTAGCGGTTCCGGCGGAAGCACTTACATATGCCGACTCTGT GAAGGGCCCTTCAACTATCTCCGGACAACCTCCAAGAACACCCCTGT TCTCCAAATGAATTCCTGAGGGCCGAAGATAACCGCGGTGTACTACTG CGCTAGACGGGAGTGGGGGGAGAAAGCTGGCTTCTGACTACTGGG GACAGGGCACTCTGTGACTGTCTCCGGTGGTGGATCGGGGG GTGGTGGTTCCGGGGAGGAGGATCTGGAGGAGGAGGGCTGGACATT CAAATGACTCAGTCCCGCTCCCTCCCTCCGGCTCCGGGAGATCGC GTCACGATCACGTGCAGGGCAGCAGACATCTCCAGCTACCTGAAC TGGTACCAAGCAGAACGGCAAGGGACCGAACGAAAGCTCTGATCTACGC CGCTAGCTCGTGCAGTCGGCGTCCCTCACGGTTCTCGGGATCGGG CTCAGGCACCGACTTACCCCTGACCATAGCAGCCTGAGCCGGAGGA CTTCGCGACATACTACTGTCAGCAGTCATACTCCACCCCTGACCTTC GGCAAGGGACAAAGTGGAGATCAAGAACCAACTACCCCTAGCAGCAG GCCACCCACCCCGCTCTTACCATCGCCCTCCAGCCTCTGCTCCCTGC CCGGAGGAGTGAACCCCGCAGCTGGTGGGGCGTGCATACCCGGGG TCTTGACTTCCGCTGGATATCTACATTGGGCCCCCTCTGGCTTGTGACT TGGCGGGTCTGCTGCTTCACTCGTGTACACTTAAAGCAACCCCTCATGAGGCTG GTCGGAAGAGCTGCTGTACATCTTAAAGCAACCCCTCATGAGGCTG TGCAGACTACTAAAGGAGGAGCAGCTTCTCATGCCGTTCCAGAGG AGGAGGAAGGGCGCTGCGAAGCTGCGCTGAAATTAGCAGCGCAGCGA GATGCTCAGCCTACAGCAGGGCAGACCGACTCTACAAACGACT CAATCTGGTGGAGAGAGGAGTACGACGTGCTGGACAAGCGGAGAG GACGGGACCCAGAAATGGCCGGAAAGCCGCGAGAAAAGATCCCAA GAGGGCCTGTACAACGAGCTCCAAAGGATAAGATGGCAGAACGCTA TAGCGAGATTGGTATGAAAGGGAGACGAGAAGAGGAAAGGCCACG ACGGACTGTACCAAGGGACTCAGCACCGCACCAGGACACCTATGAC GCTCTTCACATGCAAGGCCCTGCGCCTCGG	

TABLE 4

Kabat CDRs of exemplary PALLAS-derived anti-BCMA molecules						
Kabat	HCDR1	HCDR2	HCDR3	LCDR1	LCDR2	LCDR3
R1B6	SYAMS (SEQ ID NO: 44)	AISGSGGSTY YADSVKG (SEQ ID NO: 45)	REWVPYDVS WYFDY (SEQ ID NO: 46)	RASQSISS YLN (SEQ ID NO: 54)	AASSL QS (SEQ ID NO: 55)	QQSYSTP LT (SEQ ID NO: 56)
R1F2	SYAMS (SEQ ID NO: 44)	AISGSGGSTY YADSVKG (SEQ ID NO: 45)	REWWYDD WYLDY (SEQ ID NO: 68)	RASQSISS YLN (SEQ ID NO: 54)	AASSL QS (SEQ ID NO: 55)	QQSYSTP LT (SEQ ID NO: 56)

TABLE 4-continued

Kabat CDRs of exemplary PALLAS-derived anti-BCMA molecules						
Kabat	HCDR1	HCDR2	HCDR3	LCDR1	LCDR2	LCDR3
R1G5	SYAMS (SEQ ID NO: 44)	AISGGGSTY YADSVKG (SEQ ID NO: 45)	REWGESW LFDY (SEQ ID NO: 76)	RASQSISS YLN (SEQ ID NO: 54)	AASSL QS (SEQ ID NO: 55)	QQSYSTP LT (SEQ ID NO: 56)
Consensus	SYAMS (SEQ ID NO: 44)	AISGGGSTY YADSVKG (SEQ ID NO: 45)	REWX1X2X3X 4X5X6WX7X8D Y, wherein X <sub>1</sub> is absent or V; X <sub>2</sub> is absent or P; X <sub>3</sub> is W or Y; X <sub>4</sub> is G, Y, or D; X <sub>5</sub> is E, D, or V; X <sub>6</sub> is S or D; X <sub>7</sub> is L or Y; and X <sub>8</sub> is For L (SEQ ID NO: 84)	RASQSISS YLN (SEQ ID NO: 54)	AASSL QS (SEQ ID NO: 55)	QQSYSTP LT (SEQ ID NO: 56)

TABLE 5

Chothia CDRs of exemplary PALLAS-derived anti-BCMA molecules						
Chothia	HCDR1	HCDR2	HCDR3	LCDR1	LCDR2	LCDR3
R1B6	GFTFSSY (SEQ ID NO: 48)	SGSGGS (SEQ REWVPYDVS WYFDY (SEQ ID NO: 46)	SQSISSY AAS (SEQ ID (SEQ ID (SEQ ID NO: 57) NO: 58) NO: 59)	SYSTPL		
R1F2	GFTFSSY (SEQ ID NO: 48)	SGSGGS (SEQ REWWYDD WYLDY (SEQ ID NO: 68)	SQSISSY AAS (SEQ ID (SEQ ID (SEQ ID NO: 57) NO: 58) NO: 59)	SYSTPL		
R1G5	GFTFSSY (SEQ ID NO: 48)	SGSGGS (SEQ REWGESW LFDY (SEQ ID NO: 76)	SQSISSY AAS (SEQ ID (SEQ ID (SEQ ID NO: 57) NO: 58) NO: 59)	SYSTPL		
Consensus	GFTFSSY (SEQ ID NO: 48)	SGSGGS (SEQ REWX <sub>1</sub> X <sub>2</sub> X <sub>3</sub> X <sub>4</sub> X <sub>5</sub> X <sub>6</sub> WX <sub>7</sub> X <sub>8</sub> D Y, wherein X <sub>1</sub> is absent or V; X <sub>2</sub> is absent or P; X <sub>3</sub> is W or Y; X <sub>4</sub> is G, Y, or D; X <sub>5</sub> is E, D, or V; X <sub>6</sub> is S or D; X <sub>7</sub> is L or Y; and X <sub>8</sub> is For L (SEQ ID NO: 84)	SQSISSY AAS (SEQ ID (SEQ ID (SEQ ID NO: 57) NO: 58) NO: 59)	SYSTPL		

TABLE 6

IMGT CDRs of exemplary PALLAS-derived anti-BCMA molecules						
IMGT	HCDR1	HCDR2	HCDR3	LCDR1	LCDR2	LCDR3
R1B6	GFTFSSYA (SEQ ID NO: 49)	ISGGGST (SEQ ID NO: 50)	ARREWPY DVSWYFDY (SEQ ID NO: 51)	QSISSY (SEQ ID (SEQ ID NO: 60)	AAS NO: 58)	QQSYSTP LT (SEQ ID NO: 56)
R1F2	GFTFSSYA (SEQ ID NO: 49)	ISGGGST (SEQ ID NO: 50)	ARREWWYD DWYLDY (SEQ ID NO: 69)	QSISSY (SEQ ID (SEQ ID NO: 60)	AAS NO: 58)	QQSYSTP LT (SEQ ID NO: 56)

TABLE 6-continued

IMGT CDRs of exemplary PALLAS-derived anti-BCMA molecules						
IMGT	HCDR1	HCDR2	HCDR3	LCDR1	LCDR2	LCDR3
R1G5	GFTFSSYA (SEQ ID NO: 49)	ISGSGGST (SEQ ID NO: 50)	ARREWWGE (SEQ ID NO: 50)	QSISSY (SEQ ID NO: 60)	AAS (SEQ ID NO: 58)	QQSYSTP (SEQ ID NO: 56)
Consensus	GFTFSSYA (SEQ ID NO: 49)	ISGSGGST (SEQ ID NO: 50)	ARREWX <sub>1</sub> X <sub>2</sub> X <sub>3</sub> X <sub>4</sub> X <sub>5</sub> X <sub>6</sub> WX <sub>7</sub> X <sub>8</sub> DY, wherein X <sub>1</sub> is absent or V; X <sub>2</sub> is absent or P; X <sub>3</sub> is W or Y; X <sub>4</sub> is G, Y, or D; X <sub>5</sub> is E, D, or V; X <sub>6</sub> is S or D; X <sub>7</sub> is L or Y; and X <sub>8</sub> is F or L (SEQ ID NO: 85)	QSISSY (SEQ ID NO: 60)	AAS (SEQ ID NO: 58)	QQSYSTP (SEQ ID NO: 56)

TABLE 7

Amino acid and nucleic acid sequences of exemplary B cell-derived anti-BCMA molecules		
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SEQ ID NO	Name/ Description	Sequence
<u>PI61</u>		
SEQ ID NO: 86	HCDR1 (Kabat)	SYGMH
SEQ ID NO: 87	HCDR2 (Kabat)	VISYDGSNKYYADSVKG
SEQ ID NO: 88	HCDR3 (Kabat)	SGYALHDDYYGLDV
SEQ ID NO: 47	HCDR1 (Chothia)	GFTFSSY
SEQ ID NO: 89	HCDR2 (Chothia)	SYDGSN
SEQ ID NO: 88	HCDR3 (Chothia)	SGYALHDDYYGLDV
SEQ ID NO: 90	HCDR1 (IMGT)	GFTFSSYG
SEQ ID NO: 91	HCDR2 (IMGT)	ISYDGSNK
SEQ ID NO: 92	HCDR3 (IMGT)	GGSGYALHDDYYGLDV
SEQ ID NO: 93	VH	QVQLQESGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKLEWVA VISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCGGS GYALHDDYYGLDVWGQGTLVTVSS
SEQ ID NO: 94	DNA VH	CAAGTCAGCTGCAGGAATC CGGTGGCGGAGTCGTGCAGCCTGGAAGG AGCCCTGAGACTCTCATGCCCGGTCAAGGTTACCTTTCTCTTACG GGATGCATTGGGTCAAGACAGGCCCGGAAAGGACTCGAATGGGTGG CTGTGATCAGCTACGACGGCTCAAACAAGTACTACGCCGACTCCGTGA AAGGCCGGTTCACTATCTCCCGGACAACTCCAAGAACACGCTGTATCT GCAAATGAATTCACTGCCCGGGAGGATACCCTGTACTACTGCCG TGGCTCCGGTTACGCCCTGCACGATGACTATTACGGCCTTGACGTCTGG GGCCAGGGAAACCTCGTGACTGTGTCCAGC
SEQ ID NO: 95	LCDR1 (Kabat)	TGTSSDVGGNYVS
SEQ ID NO: 96	LCDR2 (Kabat)	DVSNRPS

TABLE 7-continued

Amino acid and nucleic acid sequences of exemplary B cell-derived anti-BCMA molecules

SEQ ID NO	Name/Description	Sequence
SEQ ID NO: 97	LCDR3 (Kabat)	SSYTSSSTLYV
SEQ ID NO: 98	LCDR1 (Chothia)	TSSDVGGYNY
SEQ ID NO: 99	LCDR2 (Chothia)	DVS
SEQ ID NO: 100	LCDR3 (Chothia)	YTSSSTLY
SEQ ID NO: 101	LCDR1 (IMGT)	SSDVGGYNY
SEQ ID NO: 99	LCDR2 (IMGT)	DVS
SEQ ID NO: 97	LCDR3 (IMGT)	SSYTSSSTLYV
SEQ ID NO: 102	VL	QSALTQPASVGSPGQSQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIV DVSNRPSGVSNRSGSKSGNTASLTISGLQAEDEADYYCSSLTLYVFG SGTKVTVL
SEQ ID NO: 103	DNA VL	CAGAGCGCACTGACTCAGCCGGCATCCGTGTCCGGTAGCCCCGGACAG TCGATTACCATCTCCCTGTTACCCGACCTCCCTCGACGTGGAGGGTACA ACTACGTGCTGGTACCCAGCACCCAGGAAGGGCCCTAAGTTGA TGATCTACGATGTCAAACCCGCCGTCTGGAGTCTCCAACCGGTTCTC CGGCTCCAAGTCCGGCACACCCGCCGACCTGACCATTAGCGGGCTGCA AGCCGAGGATGAGGCCGACTACTACTGCTCGAGCTACACATCCTCGAG CACCTCTACGGTTCGGCTCGGGACTAACGGTACCGTGCTG
SEQ ID NO: 104	Linker	GGGGSGGGGGGGGG
SEQ ID NO: 105	scFv (VH-linker-VL)	QVQLQESGGGVVQPGRLSLSCAASGFTFSSYGMHWVRQAPGKLEWVA VISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCGGS GYALHDDYVGLDWVGQGTLVTVSSGGGGSGGGGGGGSQALTQPS VSGSPGQSQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIVDVSNRPSGV SNRSGSKSGNTASLTISGLQAEDEADYYCSSLTLYVFGSGTKVTVL
SEQ ID NO: 106	DNA scFv	CAAGTGCAGCTGCAAGGAAATCCGGTGGGGAGTCGTGCGAGCTGGAAAGG AGCCTGAGACTCTCATGCGCCGCGTCAGGGTTCACCTTTCTCCCTACG GGATGCACTGGGTCAAGACAGGCCCGGAAAGGGACTCGAATGGGTGG CTGTGATCAGCTACGAGCTCCAACAAGTACTACGCCGACTCCGTGA AAAGCCCGGTTCACTATCTCCCGGAAACTCCAAGAACACCGTGTATCT GCAAATGAATTACTGGCGCCGAGGATACCGCTGTGACTACTCGGG TGGCTCGGTTACGCCCCGACATGACTATTACGGCCTTGACGTCGG GGCCAGGGAAACCTCTGTAAGTGACTGTGTCAGCGGGTGAGGAGGTTGG GGAGGAGGATCAGGAGGGGGTGGATCGCAGAGCCACTGACTCAGCC GGCATCCCTGTCGGTACCCCGGACAGTCGATTACCATCTCTGTACC GGCACCTCTCCGACGTGGGAGGGTACAACCTACGTCGTGGTACCAAG CAGCACCCAGGAAGGCCCTAAGTTGATGATCTACGATGTGCAAAC CGCCCGTCTGGAGTCTCCAACCGGTTCTCCGCTCCAAGTCGGCAACAA CCGCCAGCCTGACCATTAGCGGGCTGCAAGCCGAGGATGAGGCCGACT ACTACTGTCGAGCTACACATCTCGAGCACCCCTACGTGTTGGCTC GGGACTAAGGTACCGTGCTG
SEQ ID NO: 107	Full CAR amino acid sequence	QVQLQESGGGVVQPGRLSLSCAASGFTFSSYGMHWVRQAPGKLEWVA VISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCGGS GYALHDDYVGLDWVGQGTLVTVSSGGGGSGGGGGGGSQALTQPS VSGSPGQSQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIVDVSNRPSGV SNRSGSKSGNTASLTISGLQAEDEADYYCSSLTLYVFGSGTKVTVL TTTAPRPPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPIA GTCGVLLLSLVITLYCKRGKKLLYIFKQPFMRPVQTTQEEDGCSRFPEEE EGGGCELRVKFERSADAPAYQQGNQLYNELNLRREEYDVLDKRRGRDP EMGGKPRRKNPQEGLYNEQDKMMAEAYSE1GMKGERRRGKGDGLYQ GLSTATKDTYDALHMQLPPR

TABLE 7-continued

Amino acid and nucleic acid sequences of exemplary B cell-derived anti-BCMA molecules

SEQ NO	ID	Name/ Description	Sequence
SEQ NO: 108	Full CAR DNA sequence	CAAGTCAGCTGCAGGAATCCGGGGAGTCGTGCAGCCTGGAAAGGAGCTGGATCGCAGACAGCTTCTCTACGGATGCATTGGGTCACTGGTCAGACAGGCCCGGAAAGGACTCGAATGGGTGGCTGTGATCAGCTACGACGGCTCCAACAAGTACTACGCCACTCCGTGA AAGGCCGGTTCACTATCTCCGGGACAACCTCAAGAACACCGTGTATCTGC GCAAATGAATTCACTGCGCGGGAGGATACCGCTGTGTTACTACTGCGG TGGCTCGGTTACGCCCTGCAAGATGACTATTACGGCCTTGACGCTCTGG GGCCAGGGAAACCTCGTGAAGTGTGACTGTGACTGTGAGCTGGAGGGAGGTTGG GGAGGAGGATCAGGAGGGGGTGGATCGCAGAGGCACACTGACTCAGCC GGCATCGTGTGGTAGCCCCGGACAGTCGATTACCATCTCTGTGACC GGCACCTCTCCGACGTTGGGAGGGTACAACCTACGTGTCGTTGAC CAGCACCCAGGAAGGCCCTAAGTTGATGACTACGATGTGTAAC CGCCCGTGTGGAGTCTCAACCGTTCTCCGGCTCCAAGTCCGGCAACA CCGCCAGCTGACCATAGCGGGCTGCAAGGCCAGGATGAGGCCGACT ACTACTGCTCGAGCTACACATCCTCGAGCACCCCTACGTGTCGGCTC GGGGACTAAAGGTACCCGTGCTGACCACTACCCAGCACGAGGCCACC CACCCCGGCTCCCTACCATCGCCCTCCAGCCTCTGCTCTGCGTCCGGAG GCATGTTAGACCCCGCAGCTGGTGGGGCGGTGCAATACCGGGGTTTGAC TTCCGCTCGGATATCTACATTTGGGCCCCCTCTGCGCTGTAATTGGGGGG TCTCGCTCTTCACTCGTGAATCACTTTAAGCAACCCCTCATGAGGCTGTCGAGACT AAAGCTGCTGTACATTTAAGCAACCCCTCATGAGGCTGTCGAGACT ACTCAAGAGGAGGAGCAGCTGGTGGGGCGGTGCAATACCGGGGTTTGAC GGCGGCTGCAACTGCGCGTGAATTACGCGCAGCGCAGATGCTCCA GCCTACCAAGCAGGGCAGAACCCAGCTTACACGAACACTCAATTGCG CGGAGAGAGGAGTACGACGCTGGACAAGCGGAGGAGGACGGGACCC AGAAATGGGGGGAGGCCGCGAGAAAAGAATCCCCAAGAGGGCTGT ACAACAGAGCTCAAAGGATAAGATGGCAGAAGGCCTATAGCGAGATTG GTATGAAAGGGAAACGCGAGAACAGGGCAAGGCCACGACGGACTGTAC CAGGGACTCAGCACCGCCACCAAGGACACCTATGACGCTCTTCACATG CAGGCCCTGCGCGCTCGG	
<u>B61-02</u>			
SEQ NO: 86	HC DR1 (Kabat)	SYGMH	
SEQ NO: 109	HC DR2 (Kabat)	VISYKGSNKYYADSVKG	
SEQ NO: 88	HC DR3 (Kabat)	SGYALHDDYYGLDV	
SEQ NO: 47	HC DR1 (Chothia)	GFTFSSY	
SEQ NO: 110	HC DR2 (Chothia)	SYKGSN	
SEQ NO: 88	HC DR3 (Chothia)	SGYALHDDYYGLDV	
SEQ NO: 90	HC DR1 (IMGT)	GFTFSSYG	
SEQ NO: 111	HC DR2 (IMGT)	ISYKGSNK	
SEQ NO: 92	HC DR3 (IMGT)	GGSGYALHDDYYGLDV	
SEQ NO: 112	VH	QVQLVESGGVVQPGRSLRLSCAASGTFSSYGMHWVRQAPGKLEWVA VISYKGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCGGS GYALHDDYYGLDWGQGTLTVTWS	
SEQ NO: 113	DNA VH	CAAGTCAGCTTGTCGAATCGGGAGGGAGTCGTGCAGCCTGGACGA TCGCTCCGGCTCTCATGTCGCGAGCGGATTCACCTCTCGAGCTACG GCATGCACTGGGTCAAGACAGGCCAGGAAGGGCTGGAAATGGGTGG CTGTCATCTCGTACAAGGGCTAAACAAAGTACTACGCCACTCCGTGAA GGGCCGGTTACCATCTCCCGGATAACTCCAAGAACACCTCTATCTG CAAATGAACAGCTGAGGGCCAGGAGTACTGCAAGTGTACTACTGCGG GGTCAGGCTACCGCGTGCACGACGACTACTACGGATTGGACGTC GGCCAAGGAACCTTGTGACCGTGTCT	

TABLE 7-continued

Amino acid and nucleic acid sequences of exemplary B cell-derived anti-BCMA molecules

SEQ ID NO	Name/Description	Sequence
SEQ ID NO: 95	LCDR1 (Kabat)	TGTSSDVGGYNYVS
SEQ ID NO: 114	LCDR2 (Kabat)	EVSNRLR
SEQ ID NO: 115	LCDR3 (Kabat)	SSYTSSSALYV
SEQ ID NO: 98	LCDR1 (Chothia)	TSSDVGGYNY
SEQ ID NO: 116	LCDR2 (Chothia)	EVS
SEQ ID NO: 117	LCDR3 (Chothia)	YTSSSALY
SEQ ID NO: 101	LCDR1 (IMGT)	SSDVGGYNY
SEQ ID NO: 116	LCDR2 (IMGT)	EVS
SEQ ID NO: 115	LCDR3 (IMGT)	SSYTSSSALYV
SEQ ID NO: 118	VL	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIV EVSNRLRGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSALYVF GSGTKVTVL
SEQ ID NO: 119	DNA VL	CAGAGCGCGCTGACTCAGCTGCCCTCCGTGAGCGGTTGCCCGGGACAG TCCATTACCATTCCTGTCACCGGGACCTCTCCGACGTGGGAGGCTACA ACTACTGTCTCTGGTACCAAGCAGCATCCGGAAAGGCCCCAAGCTGA TGATCTACGAGTGTCAACAGACTGGGGGGAGTCTCCAACCGCTTTTC CAGGTCCAAGTCCGGCACACCCGCCAGCTGACCATCAGCGGCTCCA GGCAGAAGATGAGGCTGACTATTACTGCTCTCCTACACGTCAAGCTCC GCCCTCTACGTGTTGGTCCGGGACCAAAGTCACTGTGCTG
SEQ ID NO: 63	Linker	GGGGSGGGGGGGGGGGGGGG
SEQ ID NO: 120	scFv (VH-linker-VL)	QVQLVESGGVVQPGRSRLSCAASGFTFSSYGMHWVRQAPGKLEWVA VISYKGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCGGS GYALHDDYYGLDVWGQGTLTVVSSGGGGSGGGSGGGSGGGSQSAL TQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIEVSN RLRGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSALYVFGSGT KVTVL
SEQ ID NO: 121	DNA scFv	CAAGTGCAGCTTGTCAATCGGGAGGCGGAGTGGTGCAGCCTGGACGA TCGCTGGCTCTCATGTGCCGGAGCGGATTCACCTTCTCGAGCTACG GCATGCACTGGGTCAAGACAAGGCCCAGGAAGGGCCTGGAAATGGGTGG CTGTCATCTCGTACAAGGGCTAAACAAAGTAATACGCCGACTCCGTGAA GGGCCGGTTCACCATCTCCCGGATAACTCCAAGAAATACCCCTATCTG CAAATGAAACAGCTGAGGGCCGAGGATACTGAGTGTACTACTGCGGG GGITCAGGCCTACCGCCTGCAACGACGACTACTACGGATTGGAGCTCGG GGCAGGAAACTTTGTGACCGTGTCTCTGGTGGAGCGGATCAGGG GGTGGCGGATCTGGGGTGGTTCCGGGGAGGAGGATCGCAGAGC GGCGTGAACGCTGCCCTGGTGGAGCGGATCTCCGGGAGCAGTCATT CCATTCTGTGCACCGGACCTCTCCGACGTGGAGGCTACAACACTACGT GTCTGGTACCGCAGCATCCGGAAAGGCCCGAACGCTGATGATCTA CGAAGTGTCAACAGACTGGGGAGTCTCCAACCGCTTCCGGTCC AACTCCGGCAACACCGCCAGCTGACCATCAGGGGCTCCAGGAGAA GATGAGGCTGACTATTACTGCTCTCCTACACGTCAAGCTCCGGCTCT ACGTGTTGGTCCGGGACCAAAGTCACTGTGCTG
SEQ ID NO: 122	Full CAR amino acid sequence	QVQLVESGGVVQPGRSRLSCAASGFTFSSYGMHWVRQAPGKLEWVA VISYKGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCGGS GYALHDDYYGLDVWGQGTLTVVSSGGGGSGGGSGGGSGGGSQSAL TQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIEVSN RLRGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSALYVFGSGT KVTVLTTTPAPRPPPTPAPTIASQPLSLRPEACRPAAGGAHVTRGLDFACDIYI WAPLAGTCGVLLSLVITLYCKRGRKLLYIFKQPFMRPVQTTQEEEDGCSC RFPEEEEGGCERVKFSRSADAPAYQQQONQLYNELNLGRREEYDVLDKR

TABLE 7-continued

Amino acid and nucleic acid sequences of exemplary B cell-derived anti-BCMA molecules

SEQ NO	ID	Name/ Description	Sequence
			RGRDPEMGGKPRRKNPQEGLYNELQDKMAEAYSEIGMKGERRGKGH DGLYQGLSTATKDTYDALHMQALPPR
SEQ NO: 123	Full CAR DNA sequence		CAAGTCAGCTTGTCAATCGGGAGGCGGAGTGGTGCAGCCTGGACGA TCGCTCCGGCTCTCATGTGCCGGAGCGGATTACACCTTCTCGAGCTACG GCATGCACTGGTCAGACAAGGCCAGGAAAGGGCTGGATGGGTGG CTGTCACTCGTACAAGGCTCAAACAAGTACTACGCCGACTCCGTGAA GGGCCGGTTCAACCATCTCCCGATAACTCCAAGAATACCCCTATCTG CAAATGAACAGCCTGAGGGCCGAGGATACTGCAGTGACTACTGCGGG GGTCAGGCTACCGCCTGCAAGCACGACTACCGGATTGGACGTCCTGG GGCCAAGGAACACTTGTGACCGTGTCTCGTGGAGGCGGATCAGGG GGTGGCGGATCTGGGGTGGTTCTGGGGAGGGAGGATCCAGAGC GCGCTGACTCAGCCTGCCCTCGTGAAGCGTTGCCCAGACGTCATTA CCATTCCTGCAACGGGACCTCTCGACGTGGAGGCTACAACTACGT GTCTGGTACCCAGCAGATCCCCGAAAGGCCGAAGCTGATGATCTA CGAAGTGTGAAACAGACTGGGGAGTCTCAACCGTTTCCGGGTCC AAAGTCCGGCAACACCGCCAGCCTGACCATCAGCGGGCTCAGGAGAA GATGAGGCTGACTATTACTGCTCTCTACAGTCAGCTCCGGCCTCT ACGTGTCGGTCCGGGACCAAAGTCAGTGCTGACCATCCCAGC ACCGAGGCCCCACCCGGGCTCTACCATCGCCTCCAGGCTGTGACC CTGCGTCCGGAGGAGCATGTAGACCCGCACTGGTGGGGCGTGCATACC CGGGGTCTGACTTCGCTGCGATATCTACATTGGGCCCCCTGCGCTG GTACTTGCGGGTCTGCTGCTTCACTCGTGAATCTTACTGTAAG CGCGTCCGGAGAAGCTGCTGTACATCTTAAGCAACCTCATGAGGC CTGTCAGACTACTCAAGAGGAGGACGGCTGTTCATGCCGTTCCAG AGAGGAGGAAGGCGCTGCAACTGGCGTGAATTCAGCCGCAGC GCAGATGCTCCAGCTACCGCAGGGGAGAACCGAGCTCTAACACGAA CTCAATCTGGTCCGGAGAGAGGAGTACGACGTGCTGGACAAGGGAGA GGACGGGACCAGAAATGGGGGGAGCCGCGCAGAGAAATCCCCA AGAGGGCTGTACAACGAGCTCAGGATAAGATGGCAGAAGCCTA TAGCGAGATGGTATGAAAGGGAACGCGAGAGAGGAAAGGCCACG ACCGACTGTCACAGGGACTCAGCACCCACCAAGGACACCTATGACG CTCTTCACATGCAGGCCCTGCCGCTCGG
		B61-10	
SEQ NO: 86	HCDR1 (Kabat)	SYGMH	
SEQ NO: 109	HCDR2 (Kabat)	VISYKGSNKYYADSVKG	
SEQ NO: 88	HCDR3 (Kabat)	SGYALHDDYYGLDV	
SEQ NO: 47	HCDR1 (Chothia)	GFTFSSY	
SEQ NO: 110	HCDR2 (Chothia)	SYKGSN	
SEQ NO: 88	HCDR3 (Chothia)	SGYALHDDYYGLDV	
SEQ NO: 90	HCDR1 (IMGT)	GFTFSSYG	
SEQ NO: 111	HCDR2 (IMGT)	ISYKGSNK	
SEQ NO: 92	HCDR3 (IMGT)	GGSGYALHDDYYGLDV	
SEQ NO: 112	VH	QVOLVESGGVVQPGRSLRLSCAASGPTFSSYGMHWVRQAPGKLEWVA VISYKGSNKYYADSVKGFTISRDNSKNTLYLQMNSLRAEDTAVYYCGGS GYALHDDYYGLDVWQGQGTLTVSS	
SEQ NO: 113	DNA VH	CAAGTCAGCTTGTCAATCGGGAGGCGGAGTGGTGCAGCCTGGACGA TCGCTCCGGCTCTCATGTGCCGGAGCGGATTACACCTTCTCGAGCTACG GCATGCACTGGTCAGACAAGGCCAGGAAAGGGCTGGATGGGTGG CTGTCACTCGTACAAGGCTCAAACAAGTACTACGCCGACTCCGTGAA GGGCCGGTTCAACCATCTCCCGATAACTCCAAGAATACCCCTATCTG	

TABLE 7-continued

Amino acid and nucleic acid sequences of exemplary B cell-derived anti-BCMA molecules

SEQ NO	ID	Name/ Description	Sequence
			CAAATGAACAGCCTGAGGGCGAGGATACTGCAGTGACTACTGCGGG GGTCAGGCTACGCGCTGCACGACTACTACGGATTGGACGTCTGG GGCCAAGGAACTCTTGTGACCGTGTCTCT
SEQ ID NO: 95	LCDR1	TGTSSDVGGYNYVS (Kabat)	
SEQ ID NO: 114	LCDR2	EVSNRLR (Kabat)	
SEQ ID NO: 97	LCDR3	SSYTSSSTLYV (Kabat)	
SEQ ID NO: 98	LCDR1	TSSDVGGYNY (Chothia)	
SEQ ID NO: 116	LCDR2	EVS (Chothia)	
SEQ ID NO: 100	LCDR3	YTSSSTLY (Chothia)	
SEQ ID NO: 101	LCDR1	SSDVGGYNY (IMGT)	
SEQ ID NO: 116	LCDR2	EVS (IMGT)	
SEQ ID NO: 97	LCDR3	SSYTSSSTLYV (IMGT)	
SEQ ID NO: 124	VL	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIV EVSNRLRGVSNRSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTLYVFG SGTKVTVL	
SEQ ID NO: 125	DNA VL	CAGAGCGCCTGACTCAGCTGCCCTCCGTGAGCGGTTGCCGGGACAG TCCATTACCATTTCTGTGCACCGGGACCTCTCCGACGTGGAGGCTACA ACTACGTCTCTGGTACCGAGCAGCATCCGGAAAGGCCCCAAGCTGA TGATCTACGAGTGTCAACAGACTGCGGGGAGTCTCCAACCGCTTTTC CGGGCTCAAGTCCGGCACACCCCCAGCTGACCATCAGGGCTCCA GGCAGAAGATGAGGCTGACTATTACTGCTCCTCACACGTCAAGCTCC ACCCCTACGTGTTGGTCCGGGACCAAGTCACTGTGCTG	
SEQ ID NO: 63	Linker	GGGGSGGGGGGGGGGGGGGG	
SEQ ID NO: 126	scFv (VH-linker-VL)	QPQLVESGGVVQPGRSRLSCAASGFTFSSYGMHWVRQAPGKLEWVA VISYKGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCGGS GYALHDDYYGLDVWQGQTLTVSSGGGGSGGGGGGGGGSQSAL TQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIEVSN RLRGVSNRSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTLYVFGSGTK VTVL	
SEQ ID NO: 127	DNA scFv	CAAGTGCAGCTTGTGAAATCGGGAGGCGGAGTGGTGCAGCTGGACGA TCGCTCGGCTCTCATGTGCGCGAGGGATTACCTTCTCGAGCTACG GCATGCAGCTGGGTCAAGAACGCCCAGGAAAGGGCTGGAATGGGTGG CTGTCATCTCGTACAAGGGCTAAACAAAGTACTACGCCACTCCGTGAA GGGCCGGTTACCATCTCCCGGATAACTCCAAGAAATACCTCTATCTG CAAATGAACAGCCTGAGGGCGAGGAACTGAGTGTACTACTGCGGG GGTCTCAGGCTACGCGCTGCACGACGACTACTACGGATTGGACGTCTGG GGCCAAGGAACTTTGTGACCGTGTCTGGTGGAGGGATCAGG GGTGGCGGATCTGGGGTGGTTCCGGGGAGGAGGATCGCAGAGC GCCGCTGACTCAGCCTGCCCTCGTGAAGGGTTGCCCGGGACAGTCATT CCATTCTGTGCAACGGGACCTCTCCGACGTGGGAGGCTACAACACTACGT GTCTCTGGTACCGAGCATCCCCGAAAGCCCCGAAGCTGATGATCTA CGAAGTGTGAAACAGACTGGGGAGTCTCCAACCGCTTCCGGGTCC AAAGTCGGCAACACCGGCCAGCTGACCATCAGGGCTCCAGGCAGAA GATGAGGCTGACTATTACTGCTCCTCACACGTCAAGCTCCACCCCTCT ACGTGTTGGTCCGGGACCAAGTCACTGTGCTG	
SEQ ID NO: 128	Full CAR amino acid sequence	QPQLVESGGVVQPGRSRLSCAASGFTFSSYGMHWVRQAPGKLEWVA VISYKGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCGGS GYALHDDYYGLDVWQGQTLTVSSGGGGSGGGGGGGGGSQSAL TQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIEVSN	

TABLE 7-continued

Amino acid and nucleic acid sequences of exemplary B cell-derived anti-BCMA molecules

SEQ ID NO.	Name/Description	Sequence
		RLRGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSTSLYVFGSGTK VTVLTTTPAPRPTPAPTIASQPLSLRPEACRPAAGGAHVTRGLDFACDIYI WAPLAGTCVLLSLVITLYCKRGRKLLYIFKQPFMRPVQTQEEEDGCSC RRFEEEQGCELRVKFRSADAPAYQQQQNOLYNELNLGREEYDVLDRK RGRDPEMGGKPRRKNPQEGLYNELQKD KMAEAYSEIGMKGERRGKGH DGLYQGLSTATKDTYDALHMQALPPR
SEQ ID NO: 129	Full CAR DNA sequence	CAAGTGCGACTTGTCAATCGGGAGGGCGAGTGGTGCAGCCTGGACGA TCGCTCCGCTCTCATGTGCCGCGAGCGGATTCACCTTCAGCTACG GCATGCACTGGTCAGACAAGCCCCAGGAAAGGGCTGGATGGGTGG CTGTCATCTCGTACAAGGGCTCAAACAAAGTACTACGCCGACTCCGTGAA GGGCGGGTTCAACCATCTCCCGATAACTCCAAGAATACCTCTATCTG CAAATGAACAGCCTGAGGGCCGAGGATACTGCAGTGACTACTGCGGG GGTTCAGGCTACCCGCTGCAAGCAGACTACCGGATTGGACGTCCTGG GGCAAGGAACACTTGTGACCGTGTCTCGGGAGGGAGTCAGGG GGTGCGGATCTGGGGTGGTTCCGGGGAGGGAGTCAGGAC GCGCTGACTCAGCTGCCTCCGTGAGCGGTTGCCGGGACGTCATTA CCATTTCTGTCACCCGGACCTCTCCGACGTGGAGGCTAACACTACGT GTCTGGTACACAGCATCCCCGAAAGCCCCCGAAGCTGATGATCTA CGAAGTGTGAACAGACTGGGGAGTCTCAACCGTTTCGGGTCC AAGTCGGCAACACCGCCAGCTGACCATCAGCGGGCTCAGGAGAA GATGAGGCTGACTATTACTGCTCTCTACAGCTCAAGCTCCACCTCT ACGTGTTGGGACCCGGGACCAAGGTACTGTGCTGACCCTACCCAGC ACCGAGGCCACCCACCCGGCTTACCATCGCTCCAGCTGTG CTGCGTCCGGAGGCATGTAGACCCGAGCTGGTGGGGCGTCATACC CGGGCTTGTGACTTCGCTGCGATATCTACATTGGGCCCCCTGCGCTG GTACTTGGGGTCTGCTGCTTCACTCGTGACTCTTACTGTAAG CGCGTCCGGAAGAGCTGCTGACATCTTAAGCAACCTCATGAGGC CTGTCAGACTACTCAAGAGGAGGACGGCTGTTCATGCCGTTCCAG AGGAGGAGGAAGGGCGCTGCAACTGCGGTGAAATTCAAGCCGAGC GCAGATGCTCCAGCCTACAGCAGGGGAGAACCGACTCTAACAGAA CTCATCTGGTGGAGAGAGGAGTACGACCTGCTGGACAAGCGGAGA GGACGGGGACCCAGAAAATGGGGGGAGCCGAGAACAGGAAAGGCTA AGAGGGCTGTACAACGAGCTCCAAAAGGATAAGATGGCAAGAGCTA TAGCGAGATTGGTATGAAAGGGGAACGCGAGAGAGGCAAAGGCCACG ACGACTGTACCCAGGGACTCAGCACGCCACCAAGGACACTATGACG CTCTTCACATGCGAGGCCCTGCCGCTCGG

TABLE 8

Kabat CDRs of exemplary B cell-derived anti-BCMA molecules						
Kabat	HCDR1	HCDR2	HCDR3	LCDR1	LCDR2	LCDR3
P161	SYGMH (SEQ ID NO: 86)	VISYDGSN (SEQ ID NO: 87)	SGYALHDD YYGLDV	TGTSSDV GGYNYV	DVSNRPS (SEQ ID NO: 88)	SSYTSSS TLVY (SEQ ID NO: 97)
B61-02	SYGMH (SEQ ID NO: 86)	VISYKGSN (SEQ ID NO: 109)	SGYALHDD YYGLDV	TGTSSDV GGYNYV	EVSNRLR (SEQ ID NO: 88)	SSYTSSS ALYV (SEQ ID NO: 115)
B61-10	SYGMH (SEQ ID NO: 86)	VISYKGSN (SEQ ID NO: 109)	SGYALHDD YYGLDV	TGTSSDV GGYNYV	EVSNRLR (SEQ ID NO: 88)	SSYTSSS TLVY (SEQ ID NO: 97)
Consensus	SYGMH (SEQ ID NO: 86)	VISYXGSN (SEQ ID NO: 88)	SGYALHDD YYGLDV	TGTSSDV GGYNYV	X <sub>1</sub> VSNRX <sub>2</sub> X <sub>3</sub> , wherein X <sub>1</sub> is D or E; X <sub>2</sub> is P or L; and X <sub>3</sub> is T or A (SEQ ID NO: 130)	SSYTSSS XLVY, wherein X is D or K (SEQ ID NO: 131) (SEQ ID NO: 132)

TABLE 9

Chothia CDRs of exemplary B cell-derived anti-BCMA molecules						
Chothia	HCDR1	HCDR2	HCDR3	LCDR1	LCDR2	LCDR3
PI61	GFTFSSY (SEQ ID NO: 47)	SYDGSN (SEQ ID NO: 89)	SGYALHDDY (SEQ ID NO: 88)	TSSDVGG (SEQ ID NO: 98)	DVS (SEQ ID NO: 99)	YTSSSTLY (SEQ ID NO: 100)
B61-02	GFTFSSY (SEQ ID NO: 47)	SYKGSN (SEQ ID NO: 110)	SGYALHDDY (SEQ ID NO: 88)	TSSDVGG (SEQ ID NO: 98)	EVS (SEQ ID NO: 116)	YTSSSAL Y (SEQ ID NO: 117)
B61-10	GFTFSSY (SEQ ID NO: 47)	SYKGSN (SEQ ID NO: 110)	SGYALHDDY (SEQ ID NO: 88)	TSSDVGG (SEQ ID NO: 98)	EVS (SEQ ID NO: 116)	YTSSSTLY (SEQ ID NO: 100)
Consensus	GFTFSSY (SEQ ID NO: 47)	SYXGSN, wherein X is D or K (SEQ ID NO: 133)	SGYALHDDY (SEQ ID NO: 88)	TSSDVGG (SEQ ID NO: 98)	XVS, wherein X is D or E (SEQ ID NO: 134)	YTSSSXL Y, wherein X is T or A (SEQ ID NO: 135)

TABLE 10

IMGT CDRs of exemplary B cell-derived anti-BCMA molecules						
IMGT	HCDR1	HCDR2	HCDR3	LCDR1	LCDR2	LCDR3
PI61	GFTFSSY (SEQ ID NO: 90)	ISYDGSN (SEQ ID NO: 91)	GGSGYALHDD (SEQ ID NO: 92)	SSDVGGY (SEQ ID NO: 101)	DVS (SEQ ID NO: 99)	SSYTSSSTL YV (SEQ ID NO: 97)
B61-02	GFTFSSY (SEQ ID NO: 90)	ISYKGSN (SEQ ID NO: 111)	GGSGYALHDD (SEQ ID NO: 92)	SSDVGGY (SEQ ID NO: 101)	EVS (SEQ ID NO: 116)	SSYTSSSA LYV (SEQ ID NO: 115)
B61-10	GFTFSSY (SEQ ID NO: 90)	ISYKGSN (SEQ ID NO: 111)	GGSGYALHDD (SEQ ID NO: 92)	SSDVGGY (SEQ ID NO: 101)	EVS (SEQ ID NO: 116)	SSYTSSSTL YV (SEQ ID NO: 97)
Consensus	GFTFSSY (SEQ ID NO: 90)	ISYXGSN, wherein X is D or K (SEQ ID NO: 136)	GGSGYALHDD (SEQ ID NO: 92)	SSDVGGY (SEQ ID NO: 101)	XVS, wherein X is D or E (SEQ ID NO: 134)	SSYTSSSX LYV, T or A (SEQ ID NO: 132)

TABLE 11

Amino acid and nucleic acid sequences of exemplary anti-BCMA molecules based on PI61		
Identification	Protein sequence	DNA sequence (5'-3')
Signal peptide	MALPV TALLPL ALLL HAARP (SEQ ID NO: 1)	Atggccctccctgtcacgcgtctgtgctgccgcttgcgtgtgc (SEQ ID NO: 252)
PI61 VH	QVQLQESGGGVVQPGRSLRLS CAASGFTFSSYGMHWVRQAP GKGLEWVAVISYDGSNKYYA DSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCGGSGYA LHDDYYGLDVWGQGTLVTVS S (SEQ ID NO: 93)	CAGGTACAATTGCAGGAGTCTGGAGCGG TGTGGTGCAACCCGGTCGCAGCTTGCGCCT GAGTTGTGCTGGCTTGATTTACATTTC ATCTTACCGAATGCATTGGTACGCCAGG CACCGGGAAAGGCCTTGAATGGTGGCT GTAATTTCATACGATGGTTCCAACAAATAC TATGCTGACTCAGTCAGGGTCGATTAC ATTAGTCGGGACAACCTCAAGAACACCC TTATCTCAAATGAATTCCCTTAGACGAGA GGATACGGCGGTCTATTACTGTGGTGGCA GTGGTTATGCACTTCATGATGATTACTATG GCTTGGATGTCTGGGGCAAGGGACGCTT GTAACTGTATCCTCT (SEQ ID NO: 260)
PI61 VL	QSALTQPASVSGSPGSITISCT GTSSDVGGNYVSWYQQHPG KAPKLMIYDVSNRPSGVSNRFS	CAATCTGCTCTGACTCAACCCAGCAAGCGT ATCAGGGTACCGGGACAGAGTATTACCA TAAGTTGCACGGGACCTCTAGCGATGTA

TABLE 11-continued

Amino acid and nucleic acid sequences of exemplary anti-BCMA molecules based on PI61		
Identification	Protein sequence	DNA sequence (5'-3')
	GSKSGNTASLTISLQAEDEAD YYCSSLTSSSTLYVFGSGTKVT VL (SEQ ID NO: 102)	GGGGGGTATAATTATGATCTGGTATCAA CAACACCCCGGAAAGGCCCTAAATTGAT GATCTACGACGTGAGCAATCGACCTAGTG GCGTATCAAATCGCTCTCTGCTAGCAAGA GTGGGAATACGGCGTCCTTAATTTAGCG GATTGCAAGCAGAAGATGAGGCCGATTAC TACTGCAGCTCTATACTAGCTTCTAC TTGTACGTCTTGGGAGCGGAACAAAAGT AACAGTACTC (SEQ ID NO: 261)
Linker	GGGGSGGGGGGGGS (SEQ ID NO: 104)	
ScFv PI61	QPQLQESGGGVVQPGRSRLS CAASGFTFSYYGMHWVRQAP GKGLIEWAVIYSYDGSNKYYA DSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCGGSGYA LHDYYGLDVWVGQGTLVTVS SGGGGGGGGGGGGGQSALT QPASVSGSPGQSTITISCTGTSSD VGGYNVWSVYQQHPKGAKPL MIYDVSNRPSGVSNRFSGSKSG NTASLTISLQAEDEADYYCSS YTSSSTLYVFGSGTKVT (SEQ ID NO: 105)	CaggtacaattgcaggagtctggaggccgtgtgGtgcacccggtc gcagctgcgcctgagttgtGctgegtctggatttatccatcttcatattac ggaAtgcattggtaacgcggccaggcaccggaaaggcCttgaatgg gtggctgtatccatcgcattgtTcaacaataactatgtgtactcg tcaagggtCgatttacatcggtggacaactccaagaacAccctt atcttcaaatgatcccttagagcaGaggatacgccggcttattactg tggtgccgtGtttatgcacttcatgtatgatattatggcttgGatgtct ggggcaaggacggcgttgcactgttaactgtTccctgtgggtggtagt ggtgggggaggcTccggcgggtcgcgttcaatctgtctgactC aaccagaacggcgatcagggttacccgggacagAgattaccataag ttgcacggggacctctagcGatgttaggggtataattatgtatctg gtatCaacaacacccggaaaggccctaaatgtatgtatctac gtgagcaatcgcacttgcgttgcactgttgcac agtggaaatAcggcgcccttactattagcgatttgcagcaGaag atgaggccgattactactgcagctccatActagcttttacatgtac gtctttggagcggaaacaaaactgtactc (SEQ ID NO: 253)
Transmembrane domain and hinge	TTTPAPRPTPAPTIASQPLSLR PEACRPAAGGAVHTRGLDFAC DIYIWAPLAGTCGVLLSLVIT LYC (SEQ ID NO: 202)	AcaacaacaccccccggagacgccttacaccaGccccgactatt gcgcggcagccctgcgccttgcggccgttgcggccgc gcggggcgcGcaggttcacatcggggcttgcattttgtGatatt tatattttggcttcttggcggggacaTtgtgcgttgcattttgcac ttgttattacactgtactgt (SEQ ID NO: 254)
4-1BB	KRGRKKLLYIFKQPFMRPVQT TQEEDGCSRFPREEEGGCEL (SEQ ID NO: 7)	AaacgcggggcaaaaaaaaattgtatattttAagcagccatatt aggcccgttcaacgcacgcggaggacgcgttgcattttgcagg tcccaagaagagaagaaggggctgtgaattt (SEQ ID NO: 255)
CD3zeta	RVKFSRSADAPAYQQQNQLY NELNLRREYYDVLKRRGRD PEMGKPRRKNPQEGLYNELQ KDKMAEAYSEIGMKGERRRG KGHDGLYQGLSTATKDTYDA LHMQALPPR (SEQ ID NO: 10)	CgggttaatttcaagatccgcacgcgttcaGcataccaacagg acaaaaccaactctataacGagctgaatcttggaaagaaggaggaa atgtatGtgcgttgcataacggccggcgtagagatccggagAtggcg aaaaaccaaggcgaaaaacccctcagGaggacttacaacgcac tgcagaaaacacaaaAtgcggaggcttacccggaaataggcatgaa ggcctctcaacccgcactaaggatActacgcacgcctgcacatgc aggcctgcctccgaga (SEQ ID NO: 256)
PI61 full CAR construct	MALPV TALLPLALLLHAARP QVQLQESGGGVVQPGRSRLS CAASGFTFSYYGMHWVRQAP GKGLIEWAVIYSYDGSNKYYA DSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCGGSGYA LHDYYGLDVWVGQGTLVTVS SGGGGGGGGGGGGGQSALT QPASVSGSPGQSTITISCTGTSSD VGGYNVWSVYQQHPKGAKPL MIYDVSNRPSGVSNRFSGSKSG NTASLTISLQAEDEADYYCSS YTSSSTLYVFGSGTKVT PAPRPTPAPTIASQPLSLRPEA CRPAAGGAVHTRGLDFACDIY IWAPLAGTCGVLLSLVITLYC KRGRKKLLYIFKQPFMRPVQT TQEEDGCSRFPREEEGGCEL VKFSRSADAPAYQQQNQLY NELNLRREYYDVLKRRGRD PEMGKPRRKNPQEGLYNELQ KDKMAEAYSEIGMKGERRRG KGHDGLYQGLSTATKDTYDA LHMQALPPR (SEQ ID NO: 257)	ATGGCCCTCCCTGTCAACGCTCTGTTGCTG CCGCTGCTCTGCTGCTGCCACCGCAGGGCGA CCGCAGGTACAATTGCGAGGATCTGGAGG CCGTGTGGTCAACCCCGTCGCAGCTTGC GCCTGAGTTGTGCTGCCTGCTGATTTACAT TTTCATCTTACCGAATGTCATTGGTACGCC AGGCACCGGGAAAGGCTTGAATGGGT GCTGTAATTTCATACGATGGTCCACAAA TACTATGCTGACTCAGTCAGGGTCGATT ACAATTAGTCGGGAACTCCAAGAACAC CCTTTATCTCAAATGTCATTGGTACGCC AGAGGATACGGGGCTTATTACTGTGTTG GCAGTGGTTATGCACTCATGATGATTACT ATGGCTTGGATGTCCTGGGGCAAGGGACG CTTGTAACTGTATCCTCTGGTGGTGGTGGT AGTGGTGGGGAGGCTCGGGCGTGGGG CTCTCAATCTGCTCTGACTCAACCAGCAAG CGTATCAGGGTACCCGGACAGAGTATTA CCATAAGTTGCACGGGGACCTCTAGCGAT GTAGGGGGTATAATTATGATCTTGGTAT CAACAAACCCCGGAAAGGCCCTAAATT GATGATCTACGACGTGAGCAATCGACCTA GTGGCGTATCAAATGCTTCTCTGGTAGCA AGAGTGGGAATACGGCGTCCCTACTATT ACCGGATTGCAAGCAGAAGATGAGGCCGA

TABLE 11-continued

Amino acid and nucleic acid sequences of exemplary anti-BCMA molecules based on PI61		
Identification	Protein sequence	DNA sequence (5'-3')
		TTACTACTGCAGCTCCTATACTAGCTCTTC TACATTGTACGCTTTGGAGCGGAACAA AAGTAACAGTACTACAACAAACACCTGCC CCGAGACGCCCTACACCAGCCCCGACTAT TGCCAGCCAGCCTCTGAGCCTCAGGCCCTG AGGCCCTGAGGCCAGCGGGCGGGCGA GTTCATACACGGGCTTGGATTCGCTTGT GATATTTATATTGGCTCCTTGGGGGG ACATGTGGCGTGTGTTCTGTCACTTGT ATTACACTGTACTGAAACGCCGGAAA AAAATTGCTGTATATTAAAGCAGCCATT TATGAGGCCGTTCAAGACGCCAGGAGG AGGACGGTTGCTCTTGCAAGGTTCCAGAA GAGGAAGAGGGGCTGTGAATTGCGGGT TAAATTCAAGATCCGAGACGCTCCAGC ATACCAACAGGGACAAACAAACTCTATA ACGAGCTGAATCTTGAAGAAGGGAGGAA TATGATGTGCTGGATAAACGGGGCGTAG AGATCCGGAGATGGCGGGAAAACCAAGGC GAAAAAAACCCCTCAGGAGGGACTCTAACAC GAACCTGCAAGAAAGACAAAATGGCGGAGG CTTATTCCGAAATAGGCATGAAGGGCGAG CGGAGGCAGGGAAAGGGCACGACGGAC TGTATCAAGGCCCTCAACCGGACTAAG GATAACGTACGACGCCCTGCACATGCAGGC CCTGCCTCCGAGA (SEQ ID NO: 258)
PI61 full CAR construct (Nucleic acid with signal peptide and stop codons)		ATGGCCCTCCCTGTCAACGCTCTGTTGCTGCCGC TTGCTCTGCTGCTCCACCGCACGCCGACCGCAGGT ACAATTGCAAGGAGTCCTGAGGGGGTCTGGTCAA CCGGTGGCAGCTTGCCTGAGTTGCTGCTGCGT CTGGATTACATTTCATCTTACGGAATGCATTG GTTACGCCAGGACCCGGGAAAGGGCTTGAATGG GTGGCTGTAATTTCATACGATGGTTCAAACAAAT ACTATGCTGACTCAGTCAGGGTCGATTACAT TAGTCGGGACAACCTCAAGAACACCCCTTATCTT CAAATGAAATTCCCTTAAGAGCAGAGGATACGCCGG TCTATTACTGTGGTGGCAGTGGTTATGCACTTCA TGATGATTACTATGGCTTGGATGTCCTGGGGCAA GGGACGTTGTAACTGTATCCTCTGGTGGTGGTG GTAGTGGTGGGGAGGCTCCGGCGGGTGGCGGCTC TCAATTCTCTGACTCAACACCAACCGTATCA GGGTCAACGGGACAGAGTATTACATAAGTTGCA CGGGGACCTCTAGCGATGTAGGGGGTATAATT TGTATCTGGTATCAACAAACACCCCGGAAAGCC CCTAAATTGATGATCTACGACGTGAGCAATCGAC CTAGTGGCTATCAAATCGCTCTCTGGTAGCAA GAGTGGGAATACGGCCTCCCTACTATTAGCGGA TTGCAAGCAGAAAGATGAGGGCCGATTACTATGCA GCTCCCTACTAGCTCTTACATTGTACGTCTT TGGGAGCGGAACAAAAGTACAGTACTCACAAACA ACACCTGCCCGAGACCGCCTACACCGCCCGA CTATTGCCAGCCAGCCTCTGAGCCTCAGGCCCTGA GCCCTGTAGGCCCGCAGCGGGCGCAGCTTCA ACACGGGCTTGGATTTCGTTGTGATATTATA TTTGGGCTCTTGGGGGGACATGTGGCGTGT GCTTCTGTCACTTGTATTACACTGTACTGTAAA CGCGGGCGAAAAAAATTGCTGTATAATTAAAGC AGCCATTATGAGGCCGTTAGACGACGAGGA GGAGGAGCGTTGCTCTGCAAGTTCCAGAAGAG GAAGAAGGGGGCTGTGAATTGGGGGTTAAATT CAAGATCCGAGACGCTCCAGCATACCAACAGGG ACAAAACCAACTCTATAACGAGCTGATCTTGA AGAAGGGAGGAATATGATGTGCTGGATAACCGGC GCGTAGAGATCCGGAGATGGCGGGAAAACCAAG GCGAAAAAAACCCCTCAGGAGGGACTCTACAAACGAA CTGCAGAAAGACAAAATGGCGGAGGCTTATTCCG AAATAGGCATGAAGGGCGAGCGGAGCGAGGGAA AGGGCAAGCACGGACTGTATCAAGGCCCTCAACC GCGACTAAGGATACGTACGACGCCCTGCACATGC AGGCCCTGCCCTCGAGATGATAA (SEQ ID NO: 416)
PI61 mature CAR protein	QVQLQESGGVVQPGRSLRLS CAASGFTFSSYGMHWVRQAP GKGLEWVAVISYDGSNKKYYA	caggtaacattgcggaggtctggaggcggtgtggtcaacccggtc gcagctgcgcctgagttgtgtcgctcgatggatttacatttcatcttacg aatgcattggatcgccaggaccggggaaaggccttgaatgggt

TABLE 11-continued

## Amino acid and nucleic acid sequences of exemplary anti-BCMA molecules based on PI61

Identification	Protein sequence	DNA sequence (5'-3')
	DSVKGRFTISRDNSKNTLYQ MNSLRAEDTAVYYCGGSGYA LHDYYGLDVWVGQQLTVTS SGGGSSGGGGSGGGGSALT QPASVSGSPGQSITISCTGTSSD VGGYNYVSVWYQQHPGKAPKL MIYDVSNRPSGVSNRFSGSKSG NTASLTISLQAEEDADYVYCSS YTSSSTLYVFGSGTKVTVLTTT PAPRPTPTPAPIASQPLSLRPEA CRPAAGGAHVTRGLDFACDIY IWAPLAGTCGVLLSLVITYC KRGRKKLLYIFKQPFMRPVQQT TQEEDGCSCRFPREEEGGCEL VKFSRSADAPAYQQQNOLY NELNLRREYDVLKDRRGRD PEMGKPKPRRNPNQEGLYNELQ KDKMAEAYSEIGMKGERRRG KGHDGLYQQLSTATKDTYDA LHMQLPPR (SEQ ID NO: 107)	ggctgtatattcatacgatggtccaacaaatactatgctactca agggtcattataatttagtcggacaactccaagaacacccttatctt caaataatcccttagagcagaggatcacggcggttataactgtgttg gcagtgttatgcattcatgtgatattactggctggatgtctgggg caaggacgctgtatgcattgtatccctgggtgggtatgtgtgg ggaggctccgggtggcgttcaatctgtactcaaccac aagcgatcagggtcaccgggacagattaccataatgtgac ggacttctatgcgtatgggttataattatgtatcttggatcaaca ggacttctatgcgtatgggttataattatgtatcttggatcaaca acaccggggaaaggcoctaattgtatcttggatcaaca gacactgtggcgatataatgcgttctgttagcaagatggaaata cgccgtccctactattagcgattgcaggatcggccgat actactgcgttctactatgcgttcttgcattgtacgtttggagcg gaacaaaatgttacatgcgttcttgcattgtacgtttggagcg acaccggcccgtacttgcgcggccgttgcggctcaggcctga ggcgttagggccgcgcggccgcgcgttcatacacgggcttg gatttcgttgcataattatgttgcggcttgcggggacatgtgg gtgtctttgttgcattgttgcattactgttgcgttgcggggaaaa aaaattgtgttatatttaatgcgttgcggccgttgcacacga cgcaggaggaggacgggtgtttgcaggccccagaagagaga agggggtgttaatttcaatgcgttgcgggttgcggggat agcataccaaacaggggacaaaaccactataacgcgttgc gaagaaggaggatgttgcgttgcgttgcggggat tccggagatggcgaaaaaccacttgcggggat actctacacgcactgcggggat aaataggcatgaaggccctcaaccgcgactaaggat ggactgtatcaaggccctcaaccgcgactaaggat cctgcacatgcaggccctgcctccgaga (SEQ ID NO: 259)

TABLE 11A

## Additional exemplary anti-BCMA binder sequences based on PI161

SEQ ID NO	Region	Sequence
400	VH	CAGGTGCAGCTGCAGGAGTCCGGCGGCCGTGGTGAGCCAGGCC GGTCCCTGAGACTGTTGTGCGGCCAGCGGCTTCACCTTTCTCTT ATGGCATGCACTGGGTGAGACAGGCACCTGGCAAGGGACTGGAGTG GGTGGCCGTGATCTCTACAGACGGCTTAACAAGTATTACGGCGATA GCGTGAAGGGCAGGTTCACCATCAGCCCGACAACCTCAAGAAC CTGTATCTGCAGATGAATAGCCTGCAGGGCGAGGATACCGCCGTGTA TTACTGGCGAGGCTCGGCTACGCACGACGATTATTACGGAC TGGACGTGTGGGACAGGGCACCCCTGGTACAGTGTGAGCTCC
401	VH	CAGGTGCAGCTGCAGGAGTCTGGCGAGGAGTGGTGAGCCAGGCC GGTCCCTGAGACTGTTGTGCGGCCAGCGGCTTCACATTTCAGCT ACGGATGCACTGGGTGAGACAGGCACCTGGCAAGGGACTGGAGTG GGTGGCCGTGATCTCTATGACGGCTTAACAAGTACTATGCCGATTC CGTGAAGGGCAGGTTCACCATCAGCCCGACAACCTCAAGAAC TGACTCTGCAGATGAATTCCCTGCGGGCGAGGATACCGCCGTGTA TATTGTGGCGGCTCGGCTATGCCCTGCACGACGATTACTATGGACTG GACGTGTGGGACAGGGCACCCCTGGTACAGTGTCTCT
402	VH	CAGGTGCAGCTGCAGGAGTCTGGCGAGGAGTGGTGAGCCAGGCC GGAGCCTGAGACTGTTGTGCGGCCAGCGGCTTCACCTTTAGCTCTT ATGGCATGCACTGGGTGAGACAGGCACCTGGCAAGGGACTGGAGTG GGTGGCCGTGATCTCTACAGCTACGGCTCCAACAAGTATTACGGCGATA GCGTGAAGGGCAGGTTCACCATCTCGCGACAACAGAAC CTGTATCTGCAGATGAATTCCCTGCGGGCGAGGATACCGCCGTGTA TTACTGGCGAGGCGAGCGGCTACGCACGACGATTATTACGGAC TGGACGTGTGGGACAGGGCACCCCTGGTACAGTGTCTAGC
403	VH	CAGGTGCAGCTGCAGGAGAGCGGCCGTGGTGAGCCAGGCC GGTCTCTGAGACTGAGCTGTGCGGCCAGCGGCTTCACCTTAGCTCTT ACGGATGCACTGGGTGAGACAGGCACCTGGCAAGGGACTGGAGTG GGTGGCCGTGATCTCTATGACGGCAGACAACAGTACTATGCCGATA GCGTGAAGGGCAGGTTCACCATCTCCCGGACAACCTTAAGAAC CTGTACCTGCAGATGAATAGCCTGCAGGGCGAGGATACCGCCGTGTA CTATTGCGAGGCTCGGCTATGCACGACGATTACTATGGAC TGGACGTGTGGGACAGGGCACCCCTGGTACAGTGTCTAGC
404	VH	CAGGTCCAGCTGCAGGAGAGTGGGGGGGGTGTGAGCCGGAA GAAGCCTGAGACTGTATGTGCGCATCTGGTTACTTTAGCTCCT

TABLE 11A-continued

## Additional exemplary anti-BCMA binder sequences based on PI161

SEQ ID NO	Region	Sequence
		ATGGAATGCACTGGGTGCGCCAGGCACCTGGCAAGTGCCTGGAGTGG GTGGCGTGATCTCTACGACGGCTCTAACAAAGTACTATGCCGATAG CGTGAAGGGCGGTTCACCATCAGCAGAGACAACCTCAAGAAATACAC TGTATCTCAGATGAATTCTCTGGGGCGAGGATACCCCGTGTACT ATTGTTGGAGGCTCGGCTACGCACTGACGACGATTACTATGGACTG GACGTGTGGGGACAGGGCACCCCTGGTACAGTGTCTAGC
405	VH	CAGGTC CAGCTGCAGGAATCCGGCGGAGGAGTGGTGCAGCCAGGCC GGTCTCTGAGACTGAGCTGCGCCGCTCCGGCTTCACTTTCTCTT ATGGCATGCACTGGGTGAGACAGGCCCTGGCAAGTGTCTGGAGTGG GTGGCGTGATCTCTACGACGGCAGCAACAAAGTATTACGCCGATAG CGTGAAGGGCGGTTCACCATCAGCAGAGACAACCTCAAGAAATACAC TGTATCTCAGATGAATTCCCTGCGGGCGAGGATACCCCGTGTACT ATTGTTGGAGGCTCGGCTACGCACTGACGACGATTACTATGGACTG GACGTGTGGGGACAGGGCACCCCTGGTACAGTGTCTAGC
406	VH	CAGGTC CAGCTGCAGGAATCAGGGGGGGGGTGTCCAGGCCGGAA GAAGTCTGAGACTGTCATGTGCCCATCAGGGTTTACCTTTAGCTCTT ATGGCATGCACTGGGTGAGACAGGCCCTGGCAAGTGTCTGGAGTGG GTGGCGTGATCTCTACGACGGCTCTAACAAAGTACTATGCCGATAG CGTGAAGGGCGGTTCACCATCAGCAGAGACAACCTCAAGAAATACAC TGTATCTCAGATGAATTCCCTGCGGGCGAGGATACCCCGTGTACT ATTGTTGGAGGCTCGGCTACGCACTGACGACGATTACTATGGACTG GACGTGTGGGGACAGGGCACCCCTGGTACAGTGTCTAGC
407	VH	CAGGTC CAGCTGCAGGAATCCGGCGGAGGAGTGGTGCAGCCAGGCC GGTCTCTGAGACTGAGCTGCGCCGCTCCGGCTTCACTTTCTCTT ATGGCATGCACTGGGTGAGACAGGCCCTGGCAAGTGTCTGGAGTGG GTGGCGTGATCTCTACGACGGCAGCAACAAAGTATTACGCCGATAG CGTGAAGGGCGGTTCACCATCAGCAGAGACAACCTCAAGAAATACAC TGTATCTCAGATGAATTCCCTGCGGGCGAGGATACGCCGTGTACT TACTGTGGCGGCTCTGGCTACGCCCTCATGATGATTATTATGGACTG GATGCTGTGGGGACAGGGCACCCCTGGTACAGTGTCTTTCA
408	VL	CAGTC TGCCTGACCCAGCCAGCAAGCGTGTCCGGCTCTCCGGCCA GAGCATCACAAATCTCTGACCCGACAAGCTCGACGTGGAGGCT ATAACTACGTGAGCTGGTACAGCAGCACCCAGGCAAGGCCCAAG CTGATGATCTACGACGTGAGCAACAGGCTTCTGGCGTGAGCAATCG CTTCAGCGCCTCCAAGTCTGGCAATACGCCCTCTGACAATCAGCG GCCAGGCAGAGGACGAGGAGATATTACTGCTTAGCTATACC TCCCTAGCACACACTGTACGTGTTGGCAGCGGCCACCAAGGTGACAGT GCTG
409	VL	CAGAGCGCCCTGACCCAGCCAGCAGCATCCGTGTCGGAGCCCAGGCCA GTCTATCACAAATCTCTGACCCGACAAGCTCGACGTGGAGGCT ACAACATATGTGAGCTGGTACAGCAGCACCCAGGCAAGGCCCAAG CTGATGATCTACGACGTGAGCAACAGGCTTCTGGCGTGAGCAATCG ATTCTCCGCTCTAACAGCGGCAATACGCCCTCCGACAATCTCTG CCTGCAGGCAGAGGACGAGGAGATATTACTGCTAGCTACACCT CCTCTAGCACACACTGTACGTGTTGGCAGCGGCCACCAAGGTGACAGT CTG
410	VL	CAGTC TGCCTGACCCAGCCAGCAGCATCCGTGTCGGAGCCCAGGCCA GTCCATCACAAATCTCTGACCCGACAATCTGACGTGGCGGCTA TAACTACGTGCTCTGGTACAGCAGCACCCAGGCAAGGCCCAAGC TGATGATCTACGATGTGAGCAACAGGCTTCTGGCGTGAGCAATCG TTAGCAGGCCCTAACGCTGGCAATACGCCAGGCTGACAATCTCCG CCTGCAGGCAGAGGACGAGGAGATATTACTGCTAGCTCTACACCT CTAGCTCCACACTGTACGTGTTGGCAGCGGCCACCAAGGTGACAGT CTG
411	VL	CAGAGCGCCCTGACCCAGCCAGCAGCATCCGTGTCGGAGCCCAGGCCA GTCCATCACAAATCTCTGACCCGACAATCTGACGTGGCGGCTA ACAACATACGTGAGCTGGTACAGCAGCACCCAGGCAAGGCCCAAG CTGATGATCTACGATGTGAGCAACAGGCTTCTGGCGTGAGCAATCG ATTCTCCGCTCTAACAGCGGCAATACGCCAGGCTGACAATCTCCG GCCAGGCAGAGGACGAGGAGATATTACTGCTAGCTCTACACCT AGCTCCCTACACTGTACGTGTTGGCAGCGGCCACCAAGGTGACAGT GCTG
412	VL	CAGTC TGCCTGACCCAGCCAGCAGCATCCGTGTCGGAGCCCAGGCCA GTCTATCACAAATCTCTGACCCGACAAGCTCGACGTGGCGGCT ATAACTACGTGAGCTGGTACAGCAGCACCCAGGCAAGGCCCAAG CTGATGATCTACGACGTGAGCAACAGGCTTCTGGCGTGAGCAATCG GTTAGCGGCCAGCAAGTCTGGCAATACGCCCTCCGCGTGAGCAATCG

**157**

TABLE 11A-continued

**158**Additional exemplary anti-BCMA binder sequences based on PI161

SEQ ID NO	Region	Sequence
		GCCTGCAGGCAGAGGACGGCAGATTATTACTGTAGCAGTTATACT TCAAGCTAACCCCTGTACGTGTTGGATGCGGCACTAAGGTACCGT CCTG
413	VL	CAGTCGCTCTGACCAGCCCCGTTCCGTCTCAGGGCTCCAGGACAG TCAATTACCATTAAGTGTGACAGGCACCTCATCGATGTGGCGGCTAT AACTACGTGCTCTGGTATCAGCAGCACCCAGGCAAGGCCCAAGCT GATGATCTACGACGTGAGCAACAGGCCATCTGGCGTGAGCAATCGCT TCAGCGGCTCCAAGTCTGCAATACCGCAGCCTGACAATCTCGGC CTGCAGGGCAGAGGACGAGGCAGATTACTATTGCAGCTCTATACCTC TAGCTCCACACTGTACGTGTTGGCTGTGGCACCAAGGTGACAGTGCT G
414	VL	CAGTCGCCCCGTGACCCAGCCTGCAAGCGTGTCCGGCTCTCCAGGCCA GTCTATCACAAATCAGCTGTACCGCACAGCTCCGACGTGGCGGCT ATAACTACGTGAGCTGGTATCAGCAGCACCCCTGGCAAGGCCCAAGCT CTGATGATCTACGACGTGAGCAACAGGCCCTCTGGCGTGAGCAATCG GTTACGCGGCAGCAAGTCTGGCAATACCGCCTCCCTGACAATCTCTG GCCTGCAGGCAGAGGACGAGGCAGATTACTATTGCAGCTCTACACT TCTTCAGCACACTGTATGTCTTGATGCGGAACTAAGGTCACTGTC CTG
415	VL	CAGTCGCTCTGACCAGCCCCGTTCCGTCTCAGGATCTCCAGGACAG TCTATACAAATTAGTTGACAGGAACCTCTCCGATGTGGCGGCTAT AACTACGTGCTCTGGTATCAGCAGCACCCAGGCAAGGCCCAAGCT GATGATCTACGACGTGAGCAACAGGCCCTCTGGCGTGAGCAATCGCT TCAGCGGCTCCAAGTCTGCAATACCGCAGCCTGACAATCTCGGC CTGCAGGGCAGAGGACGAGGCAGATTACTATTGCAGCTCTATACCTC TAGCTCCACACTGTACGTGTTGGCTGTGGCACCAAGGTGACAGTGCT G
SEQ ID NO: 93	Anti- BCMA VH	QVQLQESGGVVQPGRLSRLSCAASGFTFSSYGMHVRQAPGKLEW VAVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYY (PI161) CGGSGYALHDDYYGLDVWGQGTLVTVSS
SEQ ID NO: 102	Anti- BCMA VL	QSALTQPASVGSPGQSITISCTGTSSDVGGYNVSWYQQHPGKAPKLM YDVSNRPSPGVSNRFSGSKSGNTASLTISGLQAEDAYYCSSYTSSSTLY (PI161) VFGSGTKVTVL
SEQ ID NO: 333	Anti- BCMA VH	QVQLQESGGVVQPGRLSRLSCAASGFTFSSYGMHVRQAPGKCLEW VAVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYY (PI161) CGGSGYALHDDYYGLDVWGQGTLVTVSS variant
SEQ ID NO: 334	Anti- BCMA VL	QSALTQPASVGSPGQSITISCTGTSSDVGGYNVSWYQQHPGKAPKLM YDVSNRPSPGVSNRFSGSKSGNTASLTISGLQAEDAYYCSSYTSSSTLY (PI161) VFGCGTKVTVL variant

TABLE 12

Amino acid and nucleic acid sequences of exemplary hybridoma-derived anti-BCMA molecules

SEQ ID NO	Name/ Description	Sequence
<u>Hy03</u>		
SEQ ID NO: 137	HCDR1 (Kabat)	GFWMS
SEQ ID NO: 138	HCDR2 (Kabat)	NIKQDGSEKYYVDSVRG
SEQ ID NO: 139	HCDR3 (Kabat)	ALDYYGMDV
SEQ ID NO: 140	HCDR1 (Chothia)	GFTFSGF

159

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TABLE 12-continued

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Amino acid and nucleic acid sequences of exemplary hybridoma-derived anti-BCMA molecules

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SEQ ID NO	Name/Description	Sequence
SEQ ID NO: 141	HCDR2 (Chothia)	KQDGSE
SEQ ID NO: 139	HCDR3 (Chothia)	ALDYYGMDV
SEQ ID NO: 142	HCDR1 (IMGT)	GFTFSGFW
SEQ ID NO: 143	HCDR2 (IMGT)	IKQDGSEK
SEQ ID NO: 144	HCDR3 (IMGT)	ARALDYYGMDV
SEQ ID NO: 145	VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFSGFWMSWVRQAPGKLEWV ANI KQDGSEKYYVD SVRGRFTI SRDNAKNSLYLQMNSLRAEDTAVYYCA RALDYYGMDVWQGTTVTVSS
SEQ ID NO: 146	DNA VH	GAAGTGCACACTGGTGGAGAGCGGTGGAGGGCTTGTCAGCCGGAGG ATCGCTGCGGGCTGTCCTGTGCTGCGTCCGGGTTCACCTCTCCGGCTTC TGGATGTCCTGGGTCAAGACAGGCACCGGGAAAGGGCTCGAATGGGT GGCCAACATCAAGCAGGATGGCTCCGAGAAGTACTACGTCGACTCCGT GAGAGGCCCTTCAACATCTCCGGGACAACCCAAGAACCTCGCTGTA CCTCCTAAATGAATAGCCTCAGGGCGGAAGATACTGCTGTATTACTG CGCACGCGCCCTTGACTACTACGGCATGGACGTCTGGGCCAAGGGAC CACTGTGACCGTGTCTAGC
SEQ ID NO: 147	LCDR1 (Kabat)	RSSQSLLSDDDGNTYLD
SEQ ID NO: 148	LCDR2 (Kabat)	TLSYRAS
SEQ ID NO: 149	LCDR3 (Kabat)	TQRLEFPSSIT
SEQ ID NO: 150	LCDR1 (Chothia)	SQSLDDSDDGNTY
SEQ ID NO: 151	LCDR2 (Chothia)	TLS
SEQ ID NO: 152	LCDR3 (Chothia)	RLEFPSSI
SEQ ID NO: 153	LCDR1 (IMGT)	QSLLDSDDGNTY
SEQ ID NO: 151	LCDR2 (IMGT)	TLS
SEQ ID NO: 149	LCDR3 (IMGT)	TQRLEFPSSIT
SEQ ID NO: 154	VL	DIVMTQTPLSLPVTPGEPA SICRSSQSLLSDDGNTYLDWYLQKPGQSPR LLIYTLSYRASGV PDRFSGSGSGTDFTLKISRVEAEDVGLYYCTQRLEFPSSIT TFGQGTRLEIK
SEQ ID NO: 155	DNA VL	GATATCGTGATGACCCAGACTCCCCCTGTCCCTGCCTGTGACTCCCGGA GAACCAAGCTCCATTCTGCCGTCTCCAGTCCTGCTGGACAGC GACGACGGCAACACTTACCTGGACTGGTACTTG CAGAAGCCGGGCCA ATCCCTCGCCCTGCTGATCTATACCCCTGTCTACCCGGGCTCAGGAGT GCCCTGACCGCTCTCGGGATCAGGGAGCGGGACCGGATTTCACCCCTGAA AATTCCCGAGTGGAAAGCCGAGGACGTGGACTGTACTACTGCACCCA GCGCCTCGAATTCCCGTCGATTACGTTGGACAGGGTACCCGGCTTGA GATCAAG
SEQ ID NO: 63	Linker	GGGGSGGGGGGGGGGGGGGG
SEQ ID NO: 156	scFv (VH-linker-VL)	EVQLVESGGGLVQPGGSLRLSCAASGFTFSGFWMSWVRQAPGKLEWV ANI KQDGSEKYYVD SVRGRFTI SRDNAKNSLYLQMNSLRAEDTAVYYCA RALDYYGMDVWQGTTVTVSSGGGGGGGGGGGGGGGGGGSDIVMTQ

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TABLE 12-continued

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Amino acid and nucleic acid sequences of exemplary hybridoma-derived anti-BCMA molecules

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SEQ ID NO	Name/Description	Sequence
		TPLSLPVTPGEPASISCRSSQSLLSDDGNTYLDWYLQKPGSPRLIYTLS YRASGVPDFRGSGSGTDFTLKISRVEAEDVGLYYCTQRLEFPSITFGQGT RLEIK
SEQ ID NO: 157	DNA scFv	GAAGTGCACACTGGTGGAGAGCCGGTGGAGGGCTTGTCAGCCGGAGG ATCGCTGCCGCTGTCCTGTGCTGCCGTTCACTTCTCCGGCTTC TGGATGTCCTGGGTCAAGACAGGACCCGGAAAGGGCTCGAATGGGT GGCCAACATCAAGCAGGATGGCTCCGAGAAAGTACTACGTCGACTCCGT GAGAGGCCGCTTCACCATCTCCGGACAACGCCAAGAACTCGCTGA CCTCCAAATGAATAGCCTCAGGGCGGAAGAGATACTGCTGTGATTACTG CGCACGCCCTTGACTACTACGGCATGGACGCTGGGGCCAAGGGAC CACTGTGACCGGTCTAGCGGAGGGCTCAGGGAGTTCAAGGGGGCGGTGGAT CAGGGGGAGGAGGATCGGGGGTGGATGGGATCGGATATCGTGTGACC CAGACTCCCCTGTCCTGCCGTGACTCCCGAGAACCGCTCCATT CCTGCCGCTCCTCCAGCTGCTGCCGACAGGACGCCAACACTT ACCTGGACTGGTACTTGCAGAACGCCGCAATCGCTCGCTGCTGA TCTATACCTGTGTCATACCGGCCCTCAGGAGTGCCTGACCGCTTCGG GATCAGGGAGCGGGACGATTCACCCGTAAAATTCCGAGTGGAA GCCAGGGAGCTGGACTGACTACTGACCCAGCGCTCGAATTCCG TCGATTACGTTGGACAGGGTACCCGGCTTGAGATCAAGACCACTACC CCAGCACCGAGGCCACCCACCCGGCTCTACCATCGCTCGCTCAGCCT CTGTCCTGCCGCGAGGCATGTAGACCCGAGCTGGTGGGGCGTG CATACCCGGGTCTTGACTTCGCTGCCGATACTCATTTGGGCCCTC TGGCTGGTACTTGCCTGGCTCGCTGCTGCTTCACTCGTGTACACTTTA CTGTAAGCGGGCTGGAAAGAGCTGCTGTACATCTTAAAGCAACCCCT CATGAGGCCGTGTCAGACTACTCAAGAGGGAGCGCTGTTATGCCG GTTCCCAGGGAGGGAGGAAGGCCGCTCGAAGTGGCTGAATTCA GCCGCAGGGAGCTGGCTCAAGCAGGGCAGAACAGCTC TACAACGAACCTAACTTGGTGCAGAGAGGAGTACGACGTGCTGGA CAAGCGGAGAGGACGGGACCAAGAAATGGGGGGAGCCGCGCAGA AAGAATCCCCAAGAGGGCTGTACACGAGCTCAAAGGATAAGAT GGCAGAACGCTATAGCGAGATGGTATGAAAGGGGAACGCGAGAAGAG GCAAGGGCCACGAGGACTGTAACAGGGACTCAGCACCGCACCAAG GACACCTATGACGCTTCACTGCAGGCCCTGCCGCTCG
SEQ ID NO: 158	Full CAR amino acid sequence	EVQLVESGGGLVQPGGSLRLSCAASGFTFSGFWMSWVRQAPKGLEWV ANIKDGSKEYVDNSVRGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCA RALDYYMDVWGGTTTVSSGGGGSGGGSGGGSDIVMTQ TPLSLPVTPGEPASISCRSSQSLLSDDGNTYLDWYLQKPGSPRLIYTLS YRASGVPDFRGSGSGTDFTLKISRVEAEDVGLYYCTQRLEFPSITFGQGT RLEIKTTTPAPRPTPAVTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYI WAPLAGTCVLLSLVITLYCKRGRKLLYIFKQPFPMPVQTQEEDGCS CRPPEEEEGGCELRVKFSRSADAPAYQQQNQLYNELNLGRREYDVL KRRGRDPMEGGKPRRNPKQEGLYNELQDKMMAEAYSEIGMKGERRRGK GHDLGYQQLSTATKDTYDALHMQALPPR
SEQ ID NO: 159	Full CAR DNA sequence	GAAGTGCACACTGGTGGAGAGCCGGTGGAGGGCTTGTCAGCCGGAGG ATCGCTGCCGCTGTCCTGTGCTGCCGTTCACTTCTCCGGCTTC TGGATGTCCTGGGTCAAGACAGGACCCGGAAAGGGCTCGAATGGGT GGCCAACATCAAGCAGGATGGCTCCGAGAAAGTACTACGTCGACTCCGT GAGAGGCCGCTTCACCATCTCCGGACAACGCCAAGAACTCGCTGA CCTCCAAATGAATAGCCTCAGGGCGGAAGAGATACTGCTGTGATTACTG CGCACGCCCTTGACTACTACGGCATGGACGCTGGGGCCAAGGGAC CACTGTGACCGGTCTAGCGGAGGGCTCAGGGGGCGGTGATCGGATATCGTGTGACC CAGACTCCCCTGTCCTGCCGTGACTCCCGAGAACCGCTCCATT CCTGCCGCTCCTCCAGCTGCTGCCGACAGGACGCCAACACTT ACCTGGACTGGTACTTGCAGAACGCCGCAATCGCTCGCTGCTGA TCTATACCTGTGTCATACCGGCCCTCAGGAGTGCCTGACCGCTTCGG GATCAGGGAGCGGGACGATTCACCCGTAAAATTCCGAGTGGAA GCCAGGGAGCTGGACTGACTACTGACCCAGCGCTCGAATTCCG TCGATTACGTTGGACAGGGTACCCGGCTTGAGATCAAGACCACTACC CCAGCACCGAGGCCACCCACCCGGCTCTACCATCGCTCGCTCAGCCT CTGTCCTGCCGCGAGGCATGTAGACCCGAGCTGGTGGGGCGTG CATACCCGGGTCTTGACTTCGCTGCCGATACTCATTTGGGCCCTC TGGCTGGTACTTGCCTGGCTCGCTGCTGCTTCACTCGTGTACACTTTA CTGTAAGCGGGCTGGAAAGAGCTGCTGTACATCTTAAAGCAACCCCT CATGAGGCCGTGTCAGACTACTCAAGAGGGAGCGCTGTTATGCCG GTTCCCAGGGAGGGAGGAAGGCCGCTCGAAGTGGCTGAATTCA GCCGCAGGGAGCTGGCTCAAGCAGGGCAGAACAGCTC TACAACGAACCTAACTTGGTGCAGAGAGGAGTACGACGTGCTGGA CAAGCGGAGAGGACGGGACCAAGAAATGGGGGGAGCCGCGCAGA AAGAATCCCCAAGAGGGCTGTACACGAGCTCAAAGGATAAGAT GGCAGAACGCTATAGCGAGATGGTATGAAAGGGGAACGCGAGAAGAG GCAAGGGCCACGAGGACTGTAACAGGGACTCAGCACCGCACCAAG GACACCTATGACGCTTCACTGCAGGCCCTGCCGCTCG

Hy52

SEQ ID NO: 160	HCDR1 (Kabat)	SFRMN
SEQ ID NO: 161	HCDR2 (Kabat)	SISSSSSYIYYADSVKG
SEQ ID NO: 162	HCDR3 (Kabat)	WLSYYGMDV

TABLE 12-continued

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Amino acid and nucleic acid sequences of exemplary hybridoma-derived anti-BCMA molecules

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SEQ ID NO	Name/Description	Sequence
SEQ ID NO: 163	HCDR1 (Chothia)	GFTFSSF
SEQ ID NO: 164	HCDR2 (Chothia)	SSSSYY
SEQ ID NO: 162	HCDR3 (Chothia)	WLSYYGMDV
SEQ ID NO: 165	HCDR1 (IMGT)	GFTFSSFR
SEQ ID NO: 166	HCDR2 (IMGT)	ISSSSSYI
SEQ ID NO: 167	HCDR3 (IMGT)	ARWLSYYGMDV
SEQ ID NO: 168	VH	EVQLVESGGGLVKPQGSRLSCAASGTFSSFRMNWVRQAPGKLEWVS SISSSSYYIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARW LSYYGMDVWGGTTTVTSS
SEQ ID NO: 169	DNA VH	GAAGTGCAACTGGTGGAGAGCGGTGGAGGGCTTGTCAAGCCGGAGG ATTCCTGCGCTGTCCCTGTGCTCGTCGGGTTCACCTCTCTCGTTC CGCATGAACTGGGTCAGACAGGCACCGGAAAGGGCTCGAATGGGT GTCCTCAATCTCATCGTCTCGTCTACATCTACTACGCCGACTCCGTG AAAGGCGCTTACCCATCTCCGGGACAACGCCAAGAACCTGCTGTAC CTCTAAATGAATAGCCTCAGGGGGAAAGATACTGCTGTATTAATGTC GCACGCTGGCTTCTACTACGGCATGGACGTCTGGGGCCAAGGGACC ACTGTGACCGTGTCTAGC
SEQ ID NO: 147	LCDR1 (Kabat)	RSSQSLLDSDDGNTYLD
SEQ ID NO: 170	LCDR2 (Kabat)	TLSFRAS
SEQ ID NO: 171	LCDR3 (Kabat)	MQRIGFPIT
SEQ ID NO: 150	LCDR1 (Chothia)	SQSLDSDDGNTY
SEQ ID NO: 151	LCDR2 (Chothia)	TLS
SEQ ID NO: 172	LCDR3 (Chothia)	RIGFPI
SEQ ID NO: 153	LCDR1 (IMGT)	QSLLDSDDGNTY
SEQ ID NO: 151	LCDR2 (IMGT)	TLS
SEQ ID NO: 171	LCDR3 (IMGT)	MQRIGFPIT
SEQ ID NO: 173	VL	DIVMTQTPLSLPVTGPGEPAISCRSSQSLLSDDGNTYLDWYLQKPGQSPQ LLIYTLSFRASGVPDFRGSGSGTDFTLKIRRVEAEDVGVYYCMQRIGFPIT FGQGTRLIEIK
SEQ ID NO: 174	DNA VL	GATATCGTGTGATGACCCAGACTCCCCCTGTCCCTGCCTGTGACTCCCGGA GAACCCAGCCTCCATTCTCGCCGTCCTCCAGTCCTGCTGGACAGC GACGACGGCAACACTTACCTGGACTGGTACTTGCAGAAGCCGGCCA ATCGCCTCAGCTGCTGATCATACCCCTGTCTATTCCGGGCTCAGGAGT GCCTGACCGCTTCTCGGGATCAGGGAGCGGGACCGATTTCACCTGAA AATTAGGCAGTGGAAAGCCGAGGACGTCGGAGTGTACTACTGCATGC AGCGCATCGGCTTCCCATTACGTTGGACAGGGTACCCGGCTTGAGA TCAAG
SEQ ID NO: 63	Linker	GGGGSGGGGGGGGGGGGGGG

TABLE 12-continued

Amino acid and nucleic acid sequences of exemplary hybridoma-derived anti-BCMA molecules

SEQ ID NO	Name/Description	Sequence
SEQ ID NO: 175	scFv (VH-linker-VL)	<pre> EVQLVESGGGLVKGGSRLSCAASGFTFSSPRMNWVRQAPGKLEWVS SISSSSYYIYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARW LSYYGMDVGQGTTVTVSSGGGGGGGGGGGGGGGGSDIVMTQTPL SLPVTGPBPASICRSSQSLIDSDDGNTYLWYLOKPGQSPQLIYTLSFRA SGVPDRFSGSGSGTDFTLKIRRVEAEDVGVYVCMQRIGFPITFGQGTRLEIK </pre>
SEQ ID NO: 176	DNA scFv	<pre> GAAGTGCACACTGGGGAGAGCGGTGGAGGGCTTGTCAAGCCGGAGG ATCGCTGCCGCTGTCCTGTGCTGCGTCGGGTTCACCTTCCTCGTTC CGCATGAACCTGGTCAGACAGCAGCCGGAAAGGGCCTCGAATGGGT GTCTCATCTCATCGTCTCGTCTACATCTACTACGCCACTCCGTG AAAGCCGCTTACCATCTCCGGACAACGCCAACGAAACTCGCTGTAC CTCCAAATGAATAGCCTCAGGGGAAAGATACTGCTGTATTACTGC GCACGCTGGCTTCTACTACCGCATGGACGCTGGGGCAAGGGACC ACTGTGACCGTGTCTAGCGGAGGGAGGTTAGGGGGCGGTGGATC AGGGGGAGGGAGTCGGGGGTGTTGGATCGGATATCGTGTGACCC AGACTCCCCCTGTCCTGTGACTCCGGAGAAACAGCTCCATTTC CTGCGGCTCTCCAGTCCCTGCTGGACAGCGACGGCAACACTTA CCTGGACTGGTACTTGCGAGAAGCCGGGCAATCGCCTCAGCTGCTGAT CTATACCTGTCTTCCGGGCTCAGGAGTGCCTGACCGCTTCCTCGG ATCAGGGAGCGGGACCGATTCAACCTGAAATTAGGCAGGTGGAAG CCGAGGACGTCGGAGTGTACTACTGCATGCAGCGCATGGCTCCGA TTACGTTGGACAGGGTACCCGGCTTGGAGATCAAGACCAACTCCAG CACCGAGGCCACCCACCCCGCTCTACCATCGCCTCCAGCTCTGT CCCTGCGTCCGGAGGAGTGTAGACCCCGAGTGGTGGGGCGTGCATA CCCGGGGCTTGTGACTTCGCTCGGATATCTACATTGGGCCCTCTGGC TGGTACTTGGGGGCTCTGCTGTTCACTCGTGTACTCTTACTGT AAGGGCGTGGAGAAGAGCTGCTGTACATCTTAAGCAACCCCTCATG AGGCGCTGTGAGACTACTCAAGAGGAGGAGGACTGCGCTGTTCATGCCGTT CCAGAGGGAGGAAGGGCGCTGCAACTGCGCTGAGAATTCAAGCCG CAGGGCAGATGCTCAGCTACAGCAGGGCAGAACCCAGCTCTACA ACGAACATCTGGTGGAGAGGAGGAGTACGACGTGCTGGACAG CGGAGAGGAGGGACCCAGAAATGGGCGGAGGCCGCGCAGAAAGA ATCCCCAAGAGGGCTGTACAACGAGCTCCAAAAGGATAAGATGGCA GAAGCCTATAAGCGAGATTGGTATGAAAGGGAGCGCAGAAGAGGCAA AGGCCACGACGGACTGTACCCAGGGACTCAGCACCGCCACCAAGGACA CCTATGACGCTCTTACATGCAGGCCCTGCCGCTCGG </pre>
SEQ ID NO: 177	Full CAR amino acid sequence	<pre> EVQLVESGGGLVKGGSRLSCAASGFTFSSPRMNWVRQAPGKLEWVS SISSSSYYIYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARW LSYYGMDVGQGTTVTVSSGGGGGGGGGGGGGGGGSDIVMTQTPL SLPVTGPBPASICRSSQSLIDSDDGNTYLWYLOKPGQSPQLIYTLSFRA SGVPDRFSGSGSGTDFTLKIRRVEAEDVGVYVCMQRIGFPITFGQGTRLEIK KTTTPAPRPPTAPTIASQPLSLPPEACRPAAGGAVHTRGLDFACDIYIWAP LAGTCGVLLSLVITLYKCRGRKLLYIFKQPFMRPVQTTQEDGCSRFP EEEFGGCELRVKFSRSADAPAYQQQNQLYNELNLRREYDVLDKRRG RDPEMGGKPRRNPKQEGLYNELOQDKMAEAYSEIGMKGERRGKHDG LYQGLSTATKDTYDALHMQLPPR </pre>
SEQ ID NO: 178	Full CAR DNA sequence	<pre> GAAGTGCACACTGGGGAGAGCGGTGGAGGGCTTGTCAAGCCGGAGG ATCGCTGCCGCTGTCCTGTGCTGCGTCGGGTTCACCTTCCTCGTTC CGCATGAACCTGGTCAGACAGCAGCCGGAAAGGGCCTCGAATGGGT GTCTCATCTCATCGTCTCGTCTACATCTACTACGCCACTCCGTG AAAGCCGCTTACCATCTCCGGACAACGCCAACGAAACTCGCTGTAC CTCCAAATGAATAGCCTCAGGGGAAAGATACTGCTGTATTACTGC GCACGCTGGCTTCTACTACCGCATGGACGCTGGGGCAAGGGACC ACTGTGACCGTGTCTAGGGGAGGGAGGTTAGGGGGCGGTGGATC AGGGGGAGGGAGTCGGGGGTGGATCGGATATCGTGTGACCC AGACTCCCCCTGTCCTGTGACTCCGGAGAAACAGCTCCATTTC CTGCGGCTCTCCAGTCCCTGCTGGACAGCGACGCGAACACTTA CCTGGACTGGTACTTGCGAGAAGCCGGGCAATCGCCTCAGCTGCTGAT CTATACCTGTCTTCCGGGCTCAGGAGTGCCTGACCGCTTCCTCGG ATCAGGGAGCGGGACCGATTCAACCTGAAATTAGGCAGGTGGAAG CCGAGGACGTCGGAGTGTACTACTGCATGCAGCGCATGGCTCCGA TTACGTTGGACAGGGTACCCGGCTTGGAGATCAAGACCAACTCCAG CACCGAGGCCACCCACCCCGCTCTACCATCGCCTCCAGCTCTGT CCCTGCGTCCGGAGGAGTGTAGACCCCGAGTGGTGGGGCGTGCATA CCCGGGGCTTGTGACTTCGCTCGGATATCTACATTGGGCCCTCTGGC TGGTACTTGGGGGCTCTGCTGTTCACTCGTGTACTCTTACTGT AAGGGCGTGGAGAAGAGCTGCTGTACATCTTAAGCAACCCCTCATG AGGCGCTGTGAGACTACTCAAGAGGAGGAGGACTGCGCTGTTCATGCCGTT CCAGAGGGAGGAAGGGCGCTGCAACTGCGCTGAGAATTCAAGCCG CAGGGCAGATGCTCAGCTACAGCAGGGCAGAACCCAGCTCTACA ACGAACATCTGGTGGAGAGGAGGAGTACGACGTGCTGGACAG CGGAGAGGAGGGACCCAGAAATGGGCGGAGGCCGCGCAGAAAGA ATCCCCAAGAGGGCTGTACAACGAGCTCCAAAAGGATAAGATGGCA GAAGCCTATAAGCGAGATTGGTATGAAAGGGAGCGCAGAAGAGGCAA AGGCCACGACGGACTGTACCCAGGGACTCAGCACCGCCACCAAGGACA CCTATGACGCTCTTACATGCAGGCCCTGCCGCTCGG </pre>

TABLE 13

Kabat CDRs of exemplary hybridoma-derived anti-BCMA molecules						
Kabat	HCDR1	HCDR2	HCDR3	LCDR1	LCDR2	LCDR3
Hy03	GFWMS (SEQ ID NO: 137)	NIKQDGSEK YYVDSVRG (SEQ ID NO: 138)	ALDYYGMD V (SEQ ID NO: 139)	RSSQSLLDS DDGNTYLD (SEQ ID NO: 147)	TLSYRA S (SEQ ID NO: 148)	TQRLEFP SIT (SEQ ID NO: 149)
Hy52	SFRMN (SEQ ID NO: 160)	SISSSSYIYY ADSVKG (SEQ ID NO: 161)	WLSYYGMD V (SEQ ID NO: 162)	RSSQSLLDS DDGNTYLD (SEQ ID NO: 147)	TLSFRAS (SEQ ID NO: 170)	MQRIGFP IT (SEQ ID NO: 171)
Consensus	X <sub>1</sub> FX <sub>2</sub> MX <sub>3</sub> , wherein X <sub>1</sub> is G or S; X <sub>2</sub> is W; and X <sub>3</sub> is S or N (SEQ ID NO: 179)	X <sub>1</sub> IX <sub>2</sub> X <sub>3</sub> X <sub>4</sub> X <sub>5</sub> X <sub>6</sub> X <sub>7</sub> YYX <sub>8</sub> DS VX <sub>9</sub> G, wherein X <sub>1</sub> is A or W; X <sub>2</sub> is N or S; and X <sub>3</sub> is K or S; X <sub>4</sub> is Q or S; X <sub>5</sub> is D or S; X <sub>6</sub> is G or S; X <sub>7</sub> is E or Y; X <sub>8</sub> is K or I; X <sub>9</sub> is V or A; and X <sub>9</sub> is R or K (SEQ ID NO: 180)	X <sub>1</sub> LX <sub>2</sub> YYGM DV, wherein X <sub>1</sub> is A or W; X <sub>2</sub> is D or R; and X <sub>3</sub> is S or N (SEQ ID NO: 181)	RSSQSLLDS DDGNTYLD (SEQ ID NO: 147)	TLSXRA S, wherein F (SEQ ID NO: 182)	X <sub>1</sub> QRX <sub>2</sub> X <sub>3</sub> , FPX <sub>4</sub> IT, wherein X <sub>1</sub> is T or M; X <sub>2</sub> is L or I; X <sub>3</sub> is E or G; and X <sub>4</sub> is S or absent (SEQ ID NO: 183)

TABLE 14

Chothia CDRs of exemplary hybridoma-derived anti-BCMA molecules						
Chothia	HCDR1	HCDR2	HCDR3	LCDR1	LCDR2	LCDR3
Hy03	GFTFSGF (SEQ ID NO: 140)	KQDGSE (SEQ ID NO: 141)	ALDYYGMD V (SEQ ID NO: 139)	SQSLLDSD DGNTY (SEQ ID NO: 150)	TLS (SEQ ID NO: 152)	RLEFPSI
Hy52	GTFSSF (SEQ ID NO: 163)	SSSSY (SEQ ID NO: 164)	WLSYYGMD V (SEQ ID NO: 162)	SQSLLDSD DGNTY (SEQ ID NO: 150)	TLS (SEQ ID NO: 172)	RIGFPI
Consensus	GFTFSXF, (SEQ ID NO: 184)	X <sub>1</sub> X <sub>2</sub> X <sub>3</sub> X <sub>4</sub> SX <sub>5</sub> , wherein X <sub>1</sub> is K or S; X <sub>2</sub> is Q or S; X <sub>3</sub> is D or S; X <sub>4</sub> is G or S; and X <sub>5</sub> is E or Y (SEQ ID NO: 185)	X <sub>1</sub> LX <sub>2</sub> YYGM DV, wherein X <sub>1</sub> is A or W; X <sub>2</sub> is D or R; and X <sub>3</sub> is S or N (SEQ ID NO: 181)	SQSLLDSD DGNTY (SEQ ID NO: 150)	TLS (SEQ ID NO: 151)	RX1X2FP X <sub>3</sub> I, wherein X <sub>1</sub> is L or I; X <sub>2</sub> is E or G; and X <sub>3</sub> is S or absent (SEQ ID NO: 186)

TABLE 15

IMGT CDRs of exemplary hybridoma-derived anti-BCMA molecules						
IMGT	HCDR1	HCDR2	HCDR3	LCDR1	LCDR2	LCDR3
Hy03	GFTFSGF W (SEQ ID NO: 142)	IKQDGSEK (SEQ ID NO: 143)	ARALDYYG MDV (SEQ ID NO: 144)	QSLLDSDD GNTY (SEQ ID NO: 153)	TLS ID NO: 151)	TQRLEFPS IT (SEQ ID NO: 149)
Hy52	GTFSSFR (SEQ ID NO: 165)	ISSSSSYI (SEQ ID NO: 166)	ARWLSSYG MDV (SEQ ID NO: 167)	QSLLDSDD GNTY (SEQ ID NO: 153)	TLS ID NO: 151)	MQRIGFPI T (SEQ ID NO: 171)

TABLE 15-continued

IMGT CDRs of exemplary hybridoma-derived anti-BCMA molecules						
IMGT	HCDR1	HCDR2	HCDR3	LCDR1	LCDR2	LCDR3
Consensus	GFTFSX <sub>1</sub> F X <sub>2</sub> , wherein X <sub>1</sub> is G or S; X <sub>1</sub> is K or S; and X <sub>2</sub> is W or R (SEQ ID NO: 187)	IX <sub>1</sub> X <sub>2</sub> X <sub>3</sub> X <sub>4</sub> SX <sub>5</sub> X <sub>6</sub> , wherein X <sub>2</sub> is Q or S; X <sub>3</sub> is D or S; X <sub>4</sub> is G or S; X <sub>5</sub> is E or Y; and X <sub>6</sub> is K or I (SEQ ID NO: 188)	ARX <sub>1</sub> LX <sub>2</sub> YY GMDV, wherein X <sub>1</sub> is ID NO: 153) X <sub>2</sub> is Q or S; A or W; and X <sub>3</sub> is D or S; X <sub>2</sub> is D or S (SEQ ID NO: 189)	QSLLDSDD GNTY (SEQ ID NO: 151)	TLS (SEQ ID NO: 151)	X <sub>1</sub> QRX <sub>2</sub> X <sub>3</sub> FPX <sub>4</sub> IT, wherein X <sub>1</sub> is T or M; X <sub>2</sub> is L or I; X <sub>3</sub> is E or G; and X <sub>4</sub> is S or absent (SEQ ID NO: 183)

TABLE 20

Amino acid and nucleic acid sequences of exemplary anti-BCMA molecules			
SEQ ID NO	Name/ Description	Sequence	
duBCM			
A. 4			
SEQ ID NO: 231	HCDR1 (Kabat)	NHGMS	
SEQ ID NO: 232	HCDR2 (Kabat)	GIVYSGSTYYAASVKG	
SEQ ID NO: 233	HCDR3 (Kabat)	HGGESDV	
SEQ ID NO: 234	HCDR1 (Chothia)	GFALSNH	
SEQ ID NO: 235	HCDR2 (Chothia)	VYSGS	
SEQ ID NO: 233	HCDR3 (Chothia)	HGGESDV	
SEQ ID NO: 236	HCDR1 (IMGT)	GFALSNHG	
SEQ ID NO: 237	HCDR2 (IMGT)	IVYSGST	
SEQ ID NO: 238	HCDR3 (IMGT)	SAHGGESDV	
SEQ ID NO: 239	VH	EVQLVESGGGLVQPGGSLRLSCAVSGFALS NHMSWVRAPGKGLEWVS GIVYSGSTYYAASVKGFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAHGG ESDVWQGQGTTVTVSS	
SEQ ID NO: 262	DNA VH	GAAGTGCATTGGTGAATCAGGGGGAGGACTTGTGCAGCCTGGAGGA TGGCTGAGACTGTCAATGTGCCGTGTCGGCTTGCCCTGTCCAACCCACG GGATGTCTGGTCCCGCCGCGCTGGAAAGGGCCTCGAATGGGTGT CGGGTATTGTGTACAGCGGTAGCACCTACTATGCCGCATCCGTGAAGGG GAGATTACCATCAGCGGGACAACCTCCAGGAACACTCTGTACCTCCAA ATGAATTGCTGAGGCCAGAGGACACTGCCATCTACTACTGCTCCGC ATGGCGGAGACTCCGACGCTGGGACAGGGACACCCTGACCGTGT CTAGC	
SEQ ID NO: 54	LCDR1 (Kabat)	RASQSISSYLN	
SEQ ID NO: 55	LCDR2 (Kabat)	AASSLQS	
SEQ ID NO: 240	LCDR3 (Kabat)	QQSYSTPYT	
SEQ ID NO: 57	LCDR1 (Chothia)	SQSISYY	

TABLE 20-continued

Amino acid and nucleic acid sequences of exemplary anti-BCMA molecules						
SEQ ID NO.	Name/Description	Sequence	AAS	VL	DNA VL	Linker
SEQ ID NO: 58	LCDR2 (Chothia)					
SEQ ID NO: 241	LCDR3 (Chothia)		SYSTPY			
SEQ ID NO: 60	LCDR1 (IMGT)		QSISYY			
SEQ ID NO: 58	LCDR2 (IMGT)		AAS			
SEQ ID NO: 240	LCDR3 (IMGT)		QQSYSTPYT			
SEQ ID NO: 242	VL	DIQLTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRSGSGSTDFTLTISSLQPEDFATYYCQQSYSTPYTFGQGTKVEIK				
SEQ ID NO: 263	DNA VL	GACATCCAGCTACCCAGTCCCCGAGCTCGCTGTCGCCCTCCGTGGGAGATCGGGTCAACCATCACGTGCCGCAGCCAGTCGATTCTCCCTACCTGAACGGTACCAACAGAAGCCCCGAAAGCCCCGAAGCTTCTCATCTACGCCGCCTCGAGCCTGCAGTCAGGAGTGCCTCACCGTTCTCGGCTCCGGTCCGGTACTGATTTCACCCCTGACCATTTCCTCCCTGCAACCCGGAGGACTTCGCTACTTACTCGCAGCAGTCGACTCCACCCCTACACTTTCGGACAAGGCACCAAGGTCGAAATCAAG				
SEQ ID NO: 243	Linker	ASGGGGSGGGGGGGGS				
SEQ ID NO: 200	scFv (VH-linker-VL)	EVQLVESGGGLVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVSIVYSGSTYYAASVKGRTTISRDNSRNTLYLQMNSLRPEDTAIYCSAHGGESDVWGGTTVTVSSASGGGGGGGGGGGGSDIQLTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRSGSGSTDFTLTISSLQPEDFATYYCQQSYSTPYTFGQGTKVEIK				
SEQ ID NO: 201	DNA scFv	GAAGTGCAATTGGTGAATCAGGGGGAGGACTTGTGCAGCTGGAGATCGCTGAGACTGTCTATGTGCCGTGTCGGCTTGTGCGCTGTCCAACACGGGATGTCCTGGGCCGCCGCCCTGGAAGGGCCTCGAATGGGTGTGGGTATTGTTGACAGCGGTAGCACCCTACTATGCCGCATCCGTGAAGGGGAGATTACCATCAGCCGGACACTCCAGGAACACTCTAACCTCAAATGAATTGCGTAGGCCAGAGGACACTGCCATCTACTACTGCTCCGCCTATGGCGAGACTTCGACGTCTGGGACAGGGGACCACCGTGACCGTGTCTAGCGGAGACTTCGAGGCGGCCAGCGGGGGCTGGTGGTTAGGGGGCGGCGGATCGGACATCCAGCTACCCAGTCGCTGTCGCCCTCGTGGAGATCGGGTACCATCACGTGCCGCCAGCCAGTCGATTTCCTGACACTGAACTGGTACCAACAGAAGCCCCGAAAGCCCCGAAGCTTCTCATCTACGCCCTGAGCTCGAGTCAGGAGTGCCTCACGTTCTCGGCTTCCGGTACTGATTTCACCCCTGACCATTTCCTCCCTGCAA CGGGAGGACTTCGCTACTTACTACTGCCAGCAGTCGACTCCACCCCTACACTTTGGACAAGGCACCAAGGTCGAAATCAAG				
SEQ ID NO: 230	Full CAR amino acid sequence	EVQLVESGGGLVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVSIVYSGSTYYAASVKGRTTISRDNSRNTLYLQMNSLRPEDTAIYCSAHGGESDVWGGTTVTVSSASGGGGGGGGGGGGSDIQLTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRSGSGSTDFTLTISSLQPEDFATYYCQQSYSTPYTFGQGTKVEIKTTTPAPRPTPAPIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFPMPVQTTQEEDGCSRFPEEEEGGCELRVKFSRSDAPAYQQGQNQLYNELNLGRREYDVLDRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGDGLYQGLSTATKDTYDALHMQALPPR				

TABLE 26

CDRs of exemplary anti-BCMA molecules						
duBCMA .4	HCDR1	HCDR2	HCDR3	LCDR1	LCDR2	LCDR3
Kabat	SEQ ID NO: 231	SEQ ID NO: 232		SEQ ID NO: 233	SEQ ID NO: 54	SEQ ID NO: 55 SEQ ID NO: 240

TABLE 26-continued

CDRs of exemplary anti-BCMA molecules							
duBCMA .4	HCDR1	HCDR2	HCDR3	LCDR1	LCDR2	LCDR3	
Chothia	SEQ ID NO: 234	SEQ ID NO: 235	SEQ ID NO: 233	SEQ ID NO: 57	SEQ ID NO: 58	SEQ ID NO: 241	
IMGT	SEQ ID NO: 236	SEQ ID NO: 237	SEQ ID NO: 238	SEQ ID NO: 60	SEQ ID NO: 58	SEQ ID NO: 240	

In some embodiments, the human anti-BCMA binding domain comprises a HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3.

In certain embodiments, the CAR molecule described herein or the anti-BCMA binding domain described herein includes:

- (1) one, two, or three light chain (LC) CDRs chosen from:
  - (i) a LC CDR1 of SEQ ID NO: 54, LC CDR2 of SEQ ID NO: 55 and LC CDR3 of SEQ ID NO: 56; and/or
  - (2) one, two, or three heavy chain (HC) CDRs from one of the following:
    - (i) a HC CDR1 of SEQ ID NO: 44, HC CDR2 of SEQ ID NO: 45 and HC CDR3 of SEQ ID NO: 84; (ii) a HC CDR1 of SEQ ID NO: 44, HC CDR2 of SEQ ID NO: 45 and HC CDR3 of SEQ ID NO: 46; (iii) a HC CDR1 of SEQ ID NO: 44, HC CDR2 of SEQ ID NO: 45 and HC CDR3 of SEQ ID NO: 68; or (iv) a HC CDR1 of SEQ ID NO: 44, HC CDR2 of SEQ ID NO: 45 and HC CDR3 of SEQ ID NO: 76.

In certain embodiments, the CAR molecule described herein or the anti-BCMA binding domain described herein includes:

- (1) one, two, or three light chain (LC) CDRs from one of the following:
  - (i) a LC CDR1 of SEQ ID NO: 95, LC CDR2 of SEQ ID NO: 131 and LC CDR3 of SEQ ID NO: 132; (ii) a LC CDR1 of SEQ ID NO: 95, LC CDR2 of SEQ ID NO: 96 and LC CDR3 of SEQ ID NO: 97; (iii) a LC CDR1 of SEQ ID NO: 95, LC CDR2 of SEQ ID NO: 114 and LC CDR3 of SEQ ID NO: 115; or (iv) a LC CDR1 of SEQ ID NO: 95, LC CDR2 of SEQ ID NO: 114 and LC CDR3 of SEQ ID NO: 97; and/or
  - (2) one, two, or three heavy chain (HC) CDRs from one of the following:
    - (i) a HC CDR1 of SEQ ID NO: 86, HC CDR2 of SEQ ID NO: 130 and HC CDR3 of SEQ ID NO: 88; (ii) a HC CDR1 of SEQ ID NO: 86, HC CDR2 of SEQ ID NO: 87 and HC CDR3 of SEQ ID NO: 88; or (iii) a HC CDR1 of SEQ ID NO: 86, HC CDR2 of SEQ ID NO: 109 and HC CDR3 of SEQ ID NO: 88.

In certain embodiments, the CAR molecule described herein or the anti-BCMA binding domain described herein includes:

- (1) one, two, or three light chain (LC) CDRs from one of the following:
  - (i) a LC CDR1 of SEQ ID NO: 147, LC CDR2 of SEQ ID NO: 182 and LC CDR3 of SEQ ID NO: 183; (ii) a LC CDR1 of SEQ ID NO: 147, LC CDR2 of SEQ ID NO: 148 and LC CDR3 of SEQ ID NO: 149; or (iii) a LC CDR1 of SEQ ID NO: 147, LC CDR2 of SEQ ID NO: 170 and LC CDR3 of SEQ ID NO: 171; and/or

(2) one, two, or three heavy chain (HC) CDRs from one of the following:

- (i) a HC CDR1 of SEQ ID NO: 179, HC CDR2 of SEQ ID NO: 180 and HC CDR3 of SEQ ID NO: 181; (ii) a HC CDR1 of SEQ ID NO: 137, HC CDR2 of SEQ ID NO: 138 and HC CDR3 of SEQ ID NO: 139; or (iii) a HC CDR1 of SEQ ID NO: 160, HC CDR2 of SEQ ID NO: 161 and HC CDR3 of SEQ ID NO: 162.

In some embodiments, the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequences of SEQ ID NOs: 44, 45, 84, 54, 55, and 56, respectively. In some embodiments, the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequences of SEQ ID NOs: 44, 45, 46, 54, 55, and 56, respectively. In some embodiments, the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequences of SEQ ID NOs: 44, 45, 68, 54, 55, and 56, respectively. In some embodiments, the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequences of SEQ ID NOs: 44, 45, 76, 54, 55, and 56, respectively.

In some embodiments, the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequences of SEQ ID NOs: 47, 48, 84, 57, 58, and 59, respectively. In some embodiments, the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequences of SEQ ID NOs: 47, 48, 46, 57, 58, and 59, respectively. In some embodiments, the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequences of SEQ ID NOs: 47, 48, 68, 57, 58, and 59, respectively. In some embodiments, the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequences of SEQ ID NOs: 47, 48, 76, 57, 58, and 59, respectively.

In some embodiments, the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequences of SEQ ID NOs: 49, 50, 85, 60, 58, and 56, respectively. In some embodiments, the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequences of SEQ ID NOs: 49, 50, 51, 60, 58, and 56, respectively. In some embodiments, the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequences of SEQ ID NOs: 49, 50, 69, 60, 58, and 56, respectively. In some embodiments, the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequences of SEQ ID NOs: 49, 50, 77, 60, 58, and 56, respectively.

In some embodiments, the human anti-BCMA binding domain comprises a scFv comprising a VH (for example, a VH described herein) and VL (for example, a VL described herein). In some embodiments, the VH is attached to the VL

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via a linker, for example, a linker described herein, for example, a linker described in Table 1. In some embodiments, the human anti-BCMA binding domain comprises a (Gly<sub>4</sub>Ser)<sub>n</sub> linker, wherein n is 1, 2, 3, 4, 5, or 6, preferably 3 or 4 (SEQ ID NO: 26). The light chain variable region and heavy chain variable region of a scFv can be, for example, in any of the following orientations: light chain variable region-linker-heavy chain variable region or heavy chain variable region-linker-light chain variable region.

In some embodiments, the anti-BCMA binding domain is a fragment, for example, a single chain variable fragment (scFv). In some embodiments, the anti-BCMA binding domain is a Fv, a Fab, a (Fab')<sub>2</sub>, or a bi-functional (for example bi-specific) hybrid antibody (for example, Lanzavecchia et al., Eur. J. Immunol. 17, 105 (1987)). In some embodiments, the antibodies and fragments thereof of the invention binds a BCMA protein with wild-type or enhanced affinity.

In some instances, scFvs can be prepared according to method known in the art (see, for example, Bird et al., (1988) Science 242:423-426 and Huston et al., (1988) Proc. Natl. Acad. Sci. USA 85:5879-5883). ScFv molecules can be produced by linking VH and VL regions together using flexible polypeptide linkers. The scFv molecules comprise a linker (for example, a Ser-Gly linker) with an optimized length and/or amino acid composition. The linker length can greatly affect how the variable regions of a scFv fold and interact. In fact, if a short polypeptide linker is employed (for example, between 5-10 amino acids) intrachain folding is prevented. Interchain folding is also required to bring the two variable regions together to form a functional epitope binding site. For examples of linker orientation and size see, for example, Hollinger et al. 1993 Proc Natl Acad. Sci. U.S.A. 90:6444-6448, U.S. Patent Application Publication Nos. 2005/0100543, 2005/0175606, 2007/0014794, and PCT publication Nos. WO2006/020258 and WO2007/024715, is incorporated herein by reference.

An scFv can comprise a linker of at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, or more amino acid residues between its VL and VH regions. The linker sequence may comprise any naturally occurring amino acid. In some embodiments, the linker sequence comprises amino acids glycine and serine. In some embodiments, the linker sequence comprises sets of glycine and serine repeats such as (Gly<sub>4</sub>Ser)<sub>n</sub>, where n is a positive integer equal to or greater than 1 (SEQ ID NO: 25). In some embodiments, the linker can be (Gly<sub>4</sub>Ser)<sub>4</sub> (SEQ ID NO: 27) or (Gly<sub>4</sub>Ser)<sub>3</sub> (SEQ ID NO: 28). Variation in the linker length may retain or enhance activity, giving rise to superior efficacy in activity studies.

#### CD20 CAR

In some embodiments, the CAR-expressing cell described herein is a CD20 CAR-expressing cell (for example, a cell expressing a CAR that binds to human CD20). In some

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embodiments, the CD20 CAR-expressing cell includes an antigen binding domain according to WO2016164731 and WO2018067992, incorporated herein by reference. Exemplary CD20-binding sequences or CD20 CAR sequences are disclosed in, for example, Tables 1-5 of WO2018067992. In some embodiments, the CD20 CAR comprises a CDR, variable region, scFv, or full-length sequence of a CD20 CAR disclosed in WO2018067992 or WO2016164731.

#### CD22 CAR

In some embodiments, the CAR-expressing cell described herein is a CD22 CAR-expressing cell (for example, a cell expressing a CAR that binds to human CD22). In some embodiments, the CD22 CAR-expressing cell includes an antigen binding domain according to WO2016164731 and WO2018067992, incorporated herein by reference. Exemplary CD22-binding sequences or CD22 CAR sequences are disclosed in, for example, Tables 6A, 6B, 7A, 7B, 7C, 8A, 8B, 9A, 9B, 10A, and 10B of WO2016164731 and Tables 6-10 of WO2018067992. In some embodiments, the CD22 CAR sequences comprise a CDR, variable region, scFv or full-length sequence of a CD22 CAR disclosed in WO2018067992 or WO2016164731.

In embodiments, the CAR molecule comprises an antigen binding domain that binds to CD22 (CD22 CAR). In some embodiments, the antigen binding domain targets human CD22. In some embodiments, the antigen binding domain includes a single chain Fv sequence as described herein.

The sequences of human CD22 CAR are provided below. In some embodiments, a human CD22 CAR is CAR22-65.

#### Human CD22 CAR scFv Sequence

(SEQ ID NO: 285)  
 EVQLQQSGPGLVKPSQTLSLTCAISGDSMLSNSDTWNWIRQSPSRGLEW  
 35 LGRTYHRSWYDDYASSVRGRVSINVDTSKNQYSLQLNAVTPEDTGVYY  
 CARVRLQDGNSWSDAFDVWGQGTMVTVSSGGGSGGGGSGGGSQSALT  
 QPASAGSPGQSVTISCTGTSSDVGGYNVWSWYQQHPGKAPKLMYDVS  
 40 NRPGVSNRFGSKSGNTASLTISGLQAEDAEADYYCSSYTSSSTLYVFG  
 TGTQLTVL

#### Human CD22 CAR Heavy Chain Variable Region

45 EVQLQQSGPGLVKPSQTLSLTCAISGDSML-  
 SNSDTWNWIRQSPSRGLEWLGRTYHRSWYDDY  
 ASSVRGRVSINVDTSKNQYSLQLNAVTPEDTGVYY-  
 CARVRLQDGNSWSDAFDVWGQGTMVT VSS (SEQ ID NO 286)

#### Human CD22 CAR Light Chain Variable Region

50 QSALTQPASAGSPGQSVTISCTGTSSDVGG-  
 YNYVSWYQQHPGKAPKLMYDVSNRPSGVSNR-  
 FSGSKSGNTASLTISGLQAEDAEADYYCSSYTSSSTLY-  
 VFGTGTQLTVL (SEQ ID NO 287)

TABLE 16

Heavy Chain Variable Domain CDRs of CD22 CAR (CAR22-65)					
Candidate	SEQ ID NO: HCDR1	SEQ ID NO: HCDR2	SEQ ID NO: HCDR3	SEQ ID NO:	
CAR22-65	GDSML 288	RTYHRSTWYDDYA 290	VRLQDGNSWSD 291		
Combined	SNSDT	SSVRG	AFDV		
	WN				
CAR22-65	SNSDT 289	RTYHRSTWYDDYA 290	VRLQDGNSWSD 291		
Kabat	WN	SSVRG	AFDV		

TABLE 17

Light Chain Variable Domain CDRs of CD22 CAR (CAR22-65). The LC CDR sequences in this table have the same sequence under the Kabat or combined definitions.

Candidate	LCDR1	SEQ	SEQ	LCDR3	SEQ
		ID NO:	ID NO:		ID NO:
CAR22-65	TGTSSDVGGNYVS	95	DVSNRPS	96	SSYTSSSTLYV
Combined					97

In some embodiments, the antigen binding domain comprises a HC CDR1, a HC CDR2, and a HC CDR3 of any heavy chain binding domain amino acid sequences listed in Table 16. In embodiments, the antigen binding domain further comprises a LC CDR1, a LC CDR2, and a LC CDR3. In embodiments, the antigen binding domain comprises a LC CDR1, a LC CDR2, and a LC CDR3 amino acid sequences listed in Table 17.

In some embodiments, the antigen binding domain comprises one, two or all of LC CDR1, LC CDR2, and LC CDR3 of any light chain binding domain amino acid sequences listed in Table 17, and one, two or all of HC CDR1, HC CDR2, and HC CDR3 of any heavy chain binding domain amino acid sequences listed in Table 16.

In some embodiments, the CDRs are defined according to the Kabat numbering scheme, the Chothia numbering scheme, or a combination thereof.

The order in which the VL and VH domains appear in the scFv can be varied (i.e., VL-VH, or VH-VL orientation), and where any of one, two, three or four copies of the “G4S” subunit (SEQ ID NO: 25), in which each subunit comprises the sequence GGGGS (SEQ ID NO: 25) (for example, (G4S)<sub>3</sub> (SEQ ID NO: 28) or (G4S)<sub>4</sub> (SEQ ID NO: 27)), can connect the variable domains to create the entirety of the scFv domain. Alternatively, the CAR construct can include, for example, a linker including the sequence GST-SGSGKPGSSEGSTKG (SEQ ID NO: 43). Alternatively, the CAR construct can include, for example, a linker including the sequence LAEAAAK (SEQ ID NO: 308). In some embodiments, the CAR construct does not include a linker between the VL and VH domains.

These clones all contained a Q/K residue change in the signal domain of the co-stimulatory domain derived from CD3zeta chain.

#### EGFR CAR

In some embodiments, the CAR-expressing cell described herein is an EGFR CAR-expressing cell (for example, a cell expressing a CAR that binds to human EGFR). In some embodiments, the CAR-expressing cell described herein is an EGFRvIII CAR-expressing cell (for example, a cell expressing a CAR that binds to human EGFRvIII). Exemplary EGFRvIII CARs can include sequences disclosed in WO2014/130657, for example, Table 2 of WO2014/130657, incorporated herein by reference.

Exemplary EGFRvIII-binding sequences or EGFR CAR sequences may comprise a CDR, a variable region, an scFv, or a full-length CAR sequence of a EGFR CAR disclosed in WO2014/130657.

#### Mesothelin CAR

In some embodiments, the CAR-expressing cell described herein is a mesothelin CAR-expressing cell (for example, a cell expressing a CAR that binds to human mesothelin). Exemplary mesothelin CARs can include sequences dis-

closed in WO2015090230 and WO2017112741, for example, Tables 2, 3, 4, and 5 of WO2017112741, incorporated herein by reference.

#### Other Exemplary CARs

In other embodiments, the CAR-expressing cells can specifically bind to CD123, for example, can include a CAR molecule (for example, any of the CAR1 to CAR8), or an antigen binding domain according to Tables 1-2 of WO 2014/130635, incorporated herein by reference. The amino acid and nucleotide sequences encoding the CD123 CAR molecules and antigen binding domains (for example, including one, two, three VH CDRs; and one, two, three VL CDRs according to Kabat or Chothia), are specified in WO 2014/130635. In other embodiments, the CAR-expressing cells can specifically bind to CD123, for example, can include a CAR molecule (for example, any of the CAR123-1 to CAR123-4 and hzCAR123-1 to hzCAR123-32), or an antigen binding domain according to Tables 2, 6, and 9 of WO2016/028896, incorporated herein by reference. The amino acid and nucleotide sequences encoding the CD123 CAR molecules and antigen binding domains (for example, including one, two, three VH CDRs; and one, two, three VL CDRs according to Kabat or Chothia), are specified in WO2016/028896.

In some embodiments, the CAR molecule comprises a CLL1 CAR described herein, for example, a CLL1 CAR described in US2016/0051651A1, incorporated herein by reference. In embodiments, the CLL1 CAR comprises an amino acid, or has a nucleotide sequence shown in US2016/0051651A1, incorporated herein by reference. In other embodiments, the CAR-expressing cells can specifically bind to CLL-1, for example, can include a CAR molecule, or an antigen binding domain according to Table 2 of WO2016/014535, incorporated herein by reference. The amino acid and nucleotide sequences encoding the CLL-1 CAR molecules and antigen binding domains (for example, including one, two, three VH CDRs; and one, two, three VL CDRs according to Kabat or Chothia), are specified in WO2016/014535.

In some embodiments, the CAR molecule comprises a CD33 CAR described herein, e.g. a CD33 CAR described in US2016/0096892A1, incorporated herein by reference. In embodiments, the CD33 CAR comprises an amino acid, or has a nucleotide sequence shown in US2016/0096892A1, incorporated herein by reference. In other embodiments, the CAR-expressing cells can specifically bind to CD33, for example, can include a CAR molecule (for example, any of CAR33-1 to CAR-33-9), or an antigen binding domain according to Table 2 or 9 of WO2016/014576, incorporated herein by reference. The amino acid and nucleotide sequences encoding the CD33 CAR molecules and antigen binding domains (for example, including one, two, three VH CDRs; and one, two, three VL CDRs according to Kabat or Chothia), are specified in WO2016/014576.

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In some embodiments, the antigen binding domain comprises one, two three (for example, all three) heavy chain CDRs, HC CDR1, HC CDR2 and HC CDR3, from an antibody described herein (for example, an antibody described in WO2015/142675, US-2015-0283178-A1, US-2016-0046724-A1, US2014/0322212A1, US2016/0068601A1, US2016/0051651A1, US2016/0096892A1, US2014/0322275A1, or WO2015/090230, incorporated herein by reference), and/or one, two, three (for example, all three) light chain CDRs, LC CDR1, LC CDR2 and LC CDR3, from an antibody described herein (for example, an antibody described in WO2015/142675, US-2015-0283178-A1, US-2016-0046724-A1, US2014/0322212A1, US2016/0068601A1, US2016/0051651A1, US2016/0096892A1, US2014/0322275A1, or WO2015/090230, incorporated herein by reference). In some embodiments, the antigen binding domain comprises a heavy chain variable region and/or a variable light chain region of an antibody listed above.

In embodiments, the antigen binding domain is an antigen binding domain described in WO2015/142675, US-2015-0283178-A1, US-2016-0046724-A1, US2014/0322212A1, US2016/0068601A1, US2016/0051651A1, US2016/0096892A1, US2014/0322275A1, or WO2015/090230, incorporated herein by reference.

In embodiments, the antigen binding domain targets BCMA and is described in US-2016-0046724-A1. In embodiments, the antigen binding domain targets CD19 and is described in US-2015-0283178-A1. In embodiments, the antigen binding domain targets CD123 and is described in US2014/0322212A1, US2016/0068601A1. In embodiments, the antigen binding domain targets CLL1 and is described in US2016/0051651A1. In embodiments, the antigen binding domain targets CD33 and is described in US2016/0096892A1.

Exemplary target antigens that can be targeted using the CAR-expressing cells, include, but are not limited to, CD19, CD123, EGFRvIII, CD33, mesothelin, BCMA, and GFR ALPHA-4, among others, as described in, for example, WO2014/153270, WO 2014/130635, WO2016/028896, WO 2014/130657, WO2016/014576, WO 2015/090230, WO2016/014565, WO2016/014535, and WO2016/025880, each of which is herein incorporated by reference in its entirety.

In other embodiments, the CAR-expressing cells can specifically bind to GFR ALPHA-4, for example, can include a CAR molecule, or an antigen binding domain according to Table 2 of WO2016/025880, incorporated herein by reference. The amino acid and nucleotide sequences encoding the GFR ALPHA-4 CAR molecules and antigen binding domains (for example, including one, two, three VH CDRs; and one, two, three VL CDRs according to Kabat or Chothia), are specified in WO2016/025880.

In some embodiments, the antigen binding domain of any of the CAR molecules described herein (for example, any of CD19, CD123, EGFRvIII, CD33, mesothelin, BCMA, and GFR ALPHA-4) comprises one, two three (for example, all three) heavy chain CDRs, HC CDR1, HC CDR2 and HC CDR3, from an antibody listed above, and/or one, two, three (for example, all three) light chain CDRs, LC CDR1, LC CDR2 and LC CDR3, from an antigen binding domain listed above. In some embodiments, the antigen binding domain comprises a heavy chain variable region and/or a variable light chain region of an antibody listed or described above.

In some embodiments, the antigen binding domain comprises one, two three (for example, all three) heavy chain CDRs, HC CDR1, HC CDR2 and HC CDR3, from an

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antibody listed above, and/or one, two, three (for example, all three) light chain CDRs, LC CDR1, LC CDR2 and LC CDR3, from an antibody listed above. In some embodiments, the antigen binding domain comprises a heavy chain variable region and/or a variable light chain region of an antibody listed or described above.

In some embodiments, the tumor antigen is a tumor antigen described in International Application WO2015/142675, filed Mar. 13, 2015, which is herein incorporated by reference in its entirety. In some embodiments, the tumor antigen is chosen from one or more of: CD19; CD123; CD22; CD30; CD171; CS-1 (also referred to as CD2 subset 1, CRACC, SLAMF7, CD319, and 19A24); C-type lectin-like molecule-1 (CLL-1 or CLECL1); CD33; epidermal growth factor receptor variant III (EGFRvIII); ganglioside G2 (GD2); ganglioside GD3 (aNeu5Ac(2-8)aNeu5Ac(2-3)bDGalp(1-4)bDGlc(1-1)Cer); TNF receptor family member B cell maturation (BCMA); Tn antigen ((Tn Ag) or (GalNAc-Ser/Thr)); prostate-specific membrane antigen (PSMA); Receptor tyrosine kinase-like orphan receptor 1 (ROR1); Fms-Like Tyrosine Kinase 3 (FLT3); Tumor-associated glycoprotein 72 (TAG72); CD38; CD44v6; Carcinoembryonic antigen (CEA); Epithelial cell adhesion molecule (EPCAM); B7H3 (CD276); KIT (CD117); Interleukin-13 receptor subunit alpha-2 (IL-13Ra2 or CD213A2); Mesothelin; Interleukin 11 receptor alpha (IL-11Ra); prostate stem cell antigen (PSCA); Protease Serine 21 (Testisin or PRSS21); vascular endothelial growth factor receptor 2 (VEGFR2); Lewis(Y) antigen; CD24; Platelet-derived growth factor receptor beta (PDGFR-beta); Stage-specific embryonic antigen-4 (SSEA-4); CD20; Folate receptor alpha; Receptor tyrosine-protein kinase ERBB2 (Her2/neu); Mucin 1, cell surface associated (MUC1); epidermal growth factor receptor (EGFR); neural cell adhesion molecule (NCAM); Prostase; prostatic acid phosphatase (PAP); elongation factor 2 mutated (ELF2M); Ephrin B2; fibroblast activation protein alpha (FAP); insulin-like growth factor 1 receptor (IGF-I receptor), carbonic anhydrase IX (CAIX); Proteasome (Prosome, Macropain) Sub-unit, Beta Type, 9 (LMP2); glycoprotein 100 (gp100); oncogene fusion protein consisting of breakpoint cluster region (BCR) and Abelson murine leukemia viral oncogene homolog 1 (Abl) (bcr-abl); tyrosinase; ephrin type-A receptor 2 (EphA2); Fucosyl GM1; sialyl Lewis adhesion molecule (sLe); ganglioside GM3 (aNeu5Ac(2-3)bDGalp(1-4)bDGlc(1-1)Cer); transglutaminase 5 (TGS5); high molecular weight-melanoma-associated antigen (HMW-MAA); o-acetyl-GD2 ganglioside (OAcGD2); Folate receptor beta; tumor endothelial marker 1 (TEM1/CD248); tumor endothelial marker 7-related (TEM7R); claudin 6 (CLDN6); thyroid stimulating hormone receptor (TSHR); G protein-coupled receptor class C group 5, member D (GPRC5D); chromosome X open reading frame 61 (CXorf61); CD97; CD179a; anaplastic lymphoma kinase (ALK); Polysialic acid; placenta-specific 1 (PLAC1); hexasaccharide portion of globoH glyceroceramide (GloboH); mammary gland differentiation antigen (NY-BR-1); uroplakin 2 (UPK2); Hepatitis A virus cellular receptor 1 (HAVCR1); adrenoceptor beta 3 (ADRB3); pannexin 3 (PANX3); G protein-coupled receptor 20 (GPR20); lymphocyte antigen 6 complex, locus K 9 (LY6K); Olfactory receptor 51E2 (OR51E2); TCR Gamma Alternate Reading Frame Protein (TARP); Wilms tumor protein (WT1); Cancer/testis antigen 1 (NY-ESO-1); Cancer/testis antigen 2 (LAGE-1a); Melanoma-associated antigen 1 (MAGE-A1); ETS translocation-variant gene 6, located on chromosome 12p (ETV6-AML); sperm protein 17 (SPA17); X Antigen Family, Member 1A (XAGE1);

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angiopoietin-binding cell surface receptor 2 (Tie 2); melanoma cancer testis antigen-1 (MAD-CT-1); melanoma cancer testis antigen-2 (MAD-CT-2); Fos-related antigen 1; tumor protein p53 (p53); p53 mutant; prostein; surviving; telomerase; prostate carcinoma tumor antigen-1 (PCTA-1 or Galectin 8), melanoma antigen recognized by T cells 1 (MelanA or MART1); Rat sarcoma (Ras) mutant; human Telomerase reverse transcriptase (hTERT); sarcoma translocation breakpoints; melanoma inhibitor of apoptosis (ML-IAP); ERG (transmembrane protease, serine 2 (TMPRSS2) ETS fusion gene); N-Acetyl glucosaminyl-transferase V (NA17); paired box protein Pax-3 (PAX3); Androgen receptor; Cyclin B1; v-myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog (MYCN); Ras Homolog Family Member C (RhOC); Tyrosinase-related protein 2 (TRP-2); Cytochrome P450 1B1 (CYP1B1); CCCTC-Binding Factor (Zinc Finger Protein)-Like (BORIS or Brother of the Regulator of Imprinted Sites), Squamous Cell Carcinoma Antigen Recognized By T Cells 3 (SART3); Paired box protein Pax-5 (PAX5); procasin binding protein sp32 (OY-TES1); lymphocyte-specific protein tyrosine kinase (LCK); A kinase anchor protein 4 (AKAP-4); synovial sarcoma, X breakpoint 2 (SSX2); Receptor for Advanced Glycation Endproducts (RAGE-1); renal ubiquitous 1 (RU1); renal ubiquitous 2 (RU2); legumain; human papilloma virus E6 (HPV E6); human papilloma virus E7 (HPV E7); intestinal carboxyl esterase; heat shock protein 70-2 mutated (mut hsp70-2); CD79a; CD79b; CD72; Leukocyte-associated immunoglobulin-like receptor 1 (LAIR1); Fc fragment of IgA receptor (FCAR or CD89); Leukocyte immunoglobulin-like receptor subfamily A member 2 (LILRA2); CD300 molecule-like family member f (CD300LF); C-type lectin domain family 12 member A (CLEC12A); bone marrow stromal cell antigen 2 (BST2); EGF-like module-containing mucin-like hormone receptor-like 2 (EMR2); lymphocyte antigen 75 (LY75); Glycan-3 (GPC3); Fc receptor-like 5 (FCRL5); and immunoglobulin lambda-like polypeptide 1 (IGLL1).

In some embodiments, the antigen binding domain comprises one, two three (for example, all three) heavy chain CDRs, HC CDR1, HC CDR2 and HC CDR3, from an antibody listed above, and/or one, two, three (for example, all three) light chain CDRs, LC CDR1, LC CDR2 and LC CDR3, from an antibody listed above. In some embodiments, the antigen binding domain comprises a heavy chain variable region and/or a variable light chain region of an antibody listed or described above.

In some embodiments, the anti-tumor antigen binding domain is a fragment, for example, a single chain variable fragment (scFv). In some embodiments, the anti-a cancer associate antigen as described herein binding domain is a Fv, a Fab, a (Fab')2, or a bi-functional (for example bi-specific) hybrid antibody (for example, Lanzavecchia et al., Eur. J. Immunol. 17, 105 (1987)). In some embodiments, the antibodies and fragments thereof of the invention binds a cancer associate antigen as described herein protein with wild-type or enhanced affinity.

In some instances, scFvs can be prepared according to a method known in the art (see, for example, Bird et al., (1988) Science 242:423-426 and Huston et al., (1988) Proc. Natl. Acad. Sci. USA 85:5879-5883). ScFv molecules can be produced by linking VH and VL regions together using flexible polypeptide linkers. The scFv molecules comprise a linker (for example, a Ser-Gly linker) with an optimized length and/or amino acid composition. The linker length can greatly affect how the variable regions of a scFv fold and interact. In fact, if a short polypeptide linker is employed

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(for example, between 5-10 amino acids) intrachain folding is prevented. Interchain folding is also required to bring the two variable regions together to form a functional epitope binding site. For examples of linker orientation and size see, for example, Hollinger et al. 1993 Proc Natl Acad. Sci. U.S.A. 90:6444-6448, U.S. Patent Application Publication Nos. 2005/0100543, 2005/0175606, 2007/0014794, and PCT publication Nos. WO2006/020258 and WO2007/024715, which are incorporated herein by reference.

An scFv can comprise a linker of at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, or more amino acid residues between its VL and VH regions. The linker sequence may comprise any naturally occurring amino acid. In some embodiments, the linker sequence comprises amino acids glycine and serine. In some embodiments, the linker sequence comprises sets of glycine and serine repeats such as (Gly<sub>n</sub>Ser)<sub>n</sub>, where n is a positive integer equal to or greater than 1 (SEQ ID NO: 25). In some embodiments, the linker can be (Gly<sub>4</sub>Ser)<sub>4</sub> (SEQ ID NO: 27) or (Gly<sub>4</sub>Ser)<sub>3</sub> (SEQ ID NO: 28). Variation in the linker length may retain or enhance activity, giving rise to superior efficacy in activity studies.

In some embodiments, the antigen binding domain is a T cell receptor ("TCR"), or a fragment thereof, for example, a single chain TCR (scTCR). Methods to make such TCRs are known in the art.

See, for example, Willemse R A et al, Gene Therapy 7: 1369-1377 (2000); Zhang T et al, Cancer Gene Ther 11: 487-496 (2004); Aggen et al, Gene Ther. 19(4):365-74 (2012) (references are incorporated herein by its entirety). For example, scTCR can be engineered that contains the V $\alpha$  and V $\beta$  genes from a T cell clone linked by a linker (for example, a flexible peptide). This approach is very useful to cancer associated target that itself is intracellular, however, a fragment of such antigen (peptide) is presented on the surface of the cancer cells by MHC.

#### Transmembrane Domain

With respect to the transmembrane domain, in various embodiments, a CAR can be designed to comprise a transmembrane domain that is attached to the extracellular domain of the CAR. A transmembrane domain can include one or more additional amino acids adjacent to the transmembrane region, for example, one or more amino acid associated with the extracellular region of the protein from which the transmembrane was derived (for example, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 up to 15 amino acids of the extracellular region) and/or one or more additional amino acids associated with the intracellular region of the protein from which the transmembrane protein is derived (for example, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 up to 15 amino acids of the intracellular region). In some embodiments, the transmembrane domain is one that is associated with one of the other domains of the CAR is used. In some instances, the transmembrane domain can be selected or modified by amino acid substitution to avoid binding of such domains to the transmembrane domains of the same or different surface membrane proteins, for example, to minimize interactions with other members of the receptor complex. In some embodiments, the transmembrane domain is capable of homodimerization with another CAR on the CAR-expressing cell, for example, CART cell, surface. In some embodiments the amino acid sequence of the transmembrane domain may be modified or substituted so as to minimize interactions with the binding domains of the native binding partner present in the same CAR-expressing cell, for example, CART.

The transmembrane domain may be derived either from a natural or from a recombinant source. Where the source is

natural, the domain may be derived from any membrane-bound or transmembrane protein. In some embodiments the transmembrane domain is capable of signaling to the intracellular domain(s) whenever the CAR has bound to a target. A transmembrane domain of particular use in this invention may include at least the transmembrane region(s) of, for example, the alpha, beta or zeta chain of T-cell receptor, CD28, CD3 epsilon, CD45, CD4, CD5, CD8 (for example, CD8 alpha, CD8 beta), CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137, CD154. In some embodiments, a transmembrane domain may include at least the transmembrane region(s) of a costimulatory molecule, for example, MHC class I molecule, TNF receptor proteins, Immunoglobulin-like proteins, cytokine receptors, integrins, signaling lymphocytic activation molecules (SLAM proteins), activating NK cell receptors, BTLA, a Toll ligand receptor, OX40, CD2, CD7, CD27, CD28, CD30, CD40, CDS, ICAM-1, LFA-1 (CD11a/CD18), 4-1BB (CD137), B7-H3, CDS, ICAM-1, ICOS (CD278), GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMP7, NKP80 (KLRF1), NKP44, NKP30, NKP46, CD19, CD4, CD8alpha, CD8beta, IL2R beta, IL2R gamma, IL7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, NKG2C, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMP4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMP6 (NTB-A, Ly108), SLAM (SLAMP1, CD150, IPO-3), BLAME (SLAMP8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, and a ligand that specifically binds with CD83.

In some instances, the transmembrane domain can be attached to the extracellular region of the CAR, for example, the antigen binding domain of the CAR, via a hinge, for example, a hinge from a human protein. For example, in some embodiments, the hinge can be a human Ig (immunoglobulin) hinge, for example, an IgG4 hinge, or a CD8a hinge. In some embodiments, the hinge or spacer comprises (for example, consists of) the amino acid sequence of SEQ ID NO: 2. In some embodiments, the transmembrane domain comprises (for example, consists of) a transmembrane domain of SEQ ID NO: 6.

In some embodiments, the hinge or spacer comprises an IgG4 hinge. For example, in some embodiments, the hinge or spacer comprises a hinge of SEQ ID NO: 3. In some embodiments, the hinge or spacer comprises a hinge encoded by the nucleotide sequence of SEQ ID NO: 14.

In some embodiments, the hinge or spacer comprises an IgD hinge. For example, in some embodiments, the hinge or spacer comprises a hinge of the amino acid sequence of SEQ ID NO: 4. In some embodiments, the hinge or spacer comprises a hinge encoded by the nucleotide sequence of SEQ ID NO: 15.

In some embodiments, the transmembrane domain may be recombinant, in which case it will comprise predominantly hydrophobic residues such as leucine and valine. In some embodiments, a triplet of phenylalanine, tryptophan and valine can be found at each end of a recombinant transmembrane domain.

Optionally, a short oligo- or polypeptide linker, between 2 and 10 amino acids in length may form the linkage between the transmembrane domain and the cytoplasmic region of the CAR. A glycine-serine doublet provides a particularly suitable linker. For example, in some embodiments, the linker comprises the amino acid sequence of SEQ

ID NO: 5. In some embodiments, the linker is encoded by a nucleotide sequence of SEQ ID NO: 16.

In some embodiments, the hinge or spacer comprises a KIR2DS2 hinge.

##### 5 Cytoplasmic Domain

The cytoplasmic domain or region of a CAR of the present invention includes an intracellular signaling domain. An intracellular signaling domain is generally responsible for activation of at least one of the normal effector functions 10 of the immune cell in which the CAR has been introduced.

Examples of intracellular signaling domains for use in the CAR of the invention include the cytoplasmic sequences of the T cell receptor (TCR) and co-receptors that act in concert 15 to initiate signal transduction following antigen receptor engagement, as well as any derivative or variant of these sequences and any recombinant sequence that has the same functional capability.

It is known that signals generated through the TCR alone 20 are insufficient for full activation of the T cell and that a secondary and/or costimulatory signal is also required. Thus, T cell activation can be said to be mediated by two distinct classes of cytoplasmic signaling sequences: those that initiate antigen-dependent primary activation through the TCR (primary intracellular signaling domains) and those that act 25 in an antigen-independent manner to provide a secondary or costimulatory signal (secondary cytoplasmic domain, for example, a costimulatory domain).

A primary signaling domain regulates primary activation 30 of the TCR complex either in a stimulatory way, or in an inhibitory way. Primary intracellular signaling domains that act in a stimulatory manner may contain signaling motifs which are known as immunoreceptor tyrosine-based activation 35 motifs or ITAMs.

Examples of ITAM containing primary intracellular signaling 35 domains that are of particular use in the invention include those of TCR zeta, FcR gamma, FcR beta, CD3 gamma, CD3 delta, CD3 epsilon, CD5, CD22, CD79a, CD79b, CD278 (also known as "ICOS"), FcεRI, DAP10, DAP12, and CD66d. In some embodiments, a CAR of the 40 invention comprises an intracellular signaling domain, for example, a primary signaling domain of CD3-zeta.

In some embodiments, a primary signaling domain comprises a modified ITAM domain, for example, a mutated ITAM domain which has altered (for example, increased or decreased) activity as compared to the native ITAM domain. In some embodiments, a primary signaling domain comprises a modified ITAM-containing primary intracellular signaling domain, for example, an optimized and/or truncated ITAM-containing primary intracellular signaling domain. In some embodiments, a primary signaling domain comprises one, two, three, four or more ITAM motifs.

Further examples of molecules containing a primary intracellular signaling domain that are of particular use in the invention include those of DAP10, DAP12, and CD32.

55 The intracellular signaling domain of the CAR can comprise the primary signaling domain, for example, CD3-zeta signaling domain, by itself or it can be combined with any other desired intracellular signaling domain(s) useful in the context of a CAR of the invention. For example, the intracellular signaling domain of the CAR can comprise a primary signaling domain, for example, CD3 zeta chain portion, and a costimulatory signaling domain. The costimulatory signaling domain refers to a portion of the CAR comprising the intracellular domain of a costimulatory molecule. A costimulatory molecule is a cell surface molecule 60 other than an antigen receptor or its ligands that is required for an efficient response of lymphocytes to an antigen.

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Examples of such molecules include MHC class I molecule, TNF receptor proteins, Immunoglobulin-like proteins, cytokine receptors, integrins, signaling lymphocytic activation molecules (SLAM proteins), activating NK cell receptors, BTLA, a Toll ligand receptor, OX40, CD2, CD7, CD27, CD28, CD30, CD40, CDS, ICAM-1, LFA-1 (CD11a/CD18), 4-1BB (CD137), B7-H3, CDS, ICAM-1, ICOS (CD278), GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD4, CD8alpha, CD8beta, IL2R beta, IL2R gamma, IL7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, NKG2C, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, and a ligand that specifically binds with CD83, and the like. For example, CD27 costimulation has been demonstrated to enhance expansion, effector function, and survival of human CART cells *in vitro* and augments human T cell persistence and antitumor activity *in vivo* (Song et al. Blood. 2012; 119(3):696-706). The intracellular signaling sequences within the cytoplasmic portion of the CAR of the invention may be linked to each other in a random or specified order. Optionally, a short oligo- or polypeptide linker, for example, between 2 and 10 amino acids (for example, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids) in length may form the linkage between intracellular signaling sequence. In some embodiments, a glycine-serine doublet can be used as a suitable linker. In some embodiments, a single amino acid, for example, an alanine, a glycine, can be used as a suitable linker.

In some embodiments, the intracellular signaling domain is designed to comprise two or more, for example, 2, 3, 4, 5, or more, costimulatory signaling domains. In some embodiments, the two or more, for example, 2, 3, 4, 5, or more, costimulatory signaling domains, are separated by a linker molecule, for example, a linker molecule described herein. In some embodiments, the intracellular signaling domain comprises two costimulatory signaling domains. In some embodiments, the linker molecule is a glycine residue. In some embodiments, the linker is an alanine residue.

In some embodiments, the intracellular signaling domain is designed to comprise the signaling domain of CD3-zeta and the signaling domain of CD28. In some embodiments, the intracellular signaling domain is designed to comprise the signaling domain of CD3-zeta and the signaling domain of 4-1BB. In some embodiments, the signaling domain of 4-1BB is a signaling domain of SEQ ID NO: 7. In some embodiments, the signaling domain of CD3-zeta is a signaling domain of SEQ ID NO: 9 (mutant CD3zeta) or SEQ ID NO: 10 (wild type human CD3zeta).

In some embodiments, the intracellular signaling domain is designed to comprise the signaling domain of CD3-zeta and the signaling domain of CD27. In some embodiments, the signaling domain of CD27 comprises the amino acid sequence of SEQ ID NO: 8. In some embodiments, the signaling domain of CD27 is encoded by the nucleic acid sequence of SEQ ID NO: 19.

In some embodiments, the intracellular is designed to comprise the signaling domain of CD3-zeta and the signaling domain of CD28. In some embodiments, the signaling domain of CD28 comprises the amino acid sequence of SEQ

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ID NO: 36. In some embodiments, the signaling domain of CD28 is encoded by the nucleic acid sequence of SEQ ID NO: 37.

In some embodiments, the intracellular is designed to comprise the signaling domain of CD3-zeta and the signaling domain of ICOS. In some embodiments, the signaling domain of ICOS comprises the amino acid sequence of SEQ ID NO: 38. In some embodiments, the signaling domain of ICOS is encoded by the nucleic acid sequence of SEQ ID NO: 39.

#### CAR Configurations Dual CARs

In an embodiment, an immune cell (e.g., a T cell or NK cell) expresses two CARs, e.g., a first CAR that binds to a first antigen and a second CAR that binds to a second antigen. In an embodiment, the first antigen and the second antigen are different. In an embodiment, the first or second antigen is chosen from an antigen expressed on B cells, an antigen expressed on acute myeloid leukemia cells, or an antigen on solid tumor cells. In an embodiment, the first or second antigen is chosen from CD10, CD19, CD20, CD22, CD34, CD123, BCMA, FLT-3, ROR1, CD79b, CD179b, CD79a, CD34, CLL-1, folate receptor beta, FLT3, EGFRvIII, mesothelin, GD2, Tn antigen, sTn antigen, Tn-O-Glycopeptides, sTn-O-Glycopeptides, PSMA, CD97, TAG72, CD44v6, CEA, EPCAM, KIT, IL-13Ra2, leguman, GD3, CD171, IL-11Ra, PSCA, MAD-CT-1, MAD-CT-2, VEGFR2, LewisY, CD24, PDGFR-beta, SSEA-4, folate receptor alpha, ERBBs (e.g., ERBB2), Her2/neu, MUC1, EGFR, NCAM, Ephrin B2, CAIX, LMP2, sLe, HMWMAA, o-acetyl-GD2, folate receptor beta, TEM1/CD248, TEM7R, FAP, Legumain, HPV E6 or E7, ML-IAP, CLDN6, TSHR, GPRC5D, ALK, Polysialic acid, Fos-related antigen, neutrophil elastase, TRP-2, CYP1B1, sperm protein 17, beta human chorionic gonadotropin, AFP, thyroglobulin, PLAC1, globoH, RAGE1, MN-CA IX, human telomerase reverse transcriptase, intestinal carboxyl esterase, mut hsp 70-2, NA-17, NY-BR-1, UPK2, HAVCR1, ADRB3, PANX3, NY-ESO-1, GPR20, Ly6k, OR51E2, TARP, GFR $\alpha$ 4, or a peptide of any of these antigens presented on MHC.

In an embodiment, the first antigen is CD19. In an embodiment, the second antigen is not CD19. In an embodiment, the second antigen is an antigen disclosed herein that is not CD19.

In an embodiment, the first antigen is BCMA. In an embodiment, the second antigen is not BCMA. In an embodiment, the second antigen is an antigen disclosed herein that is not BCMA. In an embodiment, the second antigen is chosen from an antigen expressed on B cells, an antigen expressed on acute myeloid leukemia cells, or an antigen on solid tumor cells. In an embodiment, the second antigen is chosen from CD10, CD19, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, CD79a, CD34, CLL-1, folate receptor beta, FLT3, EGFRvIII, mesothelin, GD2, Tn antigen, sTn antigen, Tn-O-Glycopeptides, sTn-O-Glycopeptides, PSMA, CD97, TAG72, CD44v6, CEA, EPCAM, KIT, IL-13Ra2, leguman, GD3, CD171, IL-11Ra, PSCA, MAD-CT-1, MAD-CT-2, VEGFR2, LewisY, CD24, PDGFR-beta, SSEA-4, folate receptor alpha, ERBBs (e.g., ERBB2), Her2/neu, MUC1, EGFR, NCAM, Ephrin B2, CAIX, LMP2, sLe, HMWMAA, o-acetyl-GD2, folate receptor beta, TEM1/CD248, TEM7R, FAP, Legumain, HPV E6 or E7, ML-IAP, CLDN6, TSHR, GPRC5D, ALK, Polysialic acid, Fos-related antigen, neutrophil elastase, TRP-2, CYP1B1, sperm protein 17, beta human chorionic gonadotropin, AFP, thyroglobulin, PLAC1, globoH, RAGE1, MN-CA IX, human telomerase reverse tran-

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scriptase, intestinal carboxyl esterase, mut hsp 70-2, NA-17, NY-BR-1, UPK2, HAVCR1, ADRB3, PANX3, NY-ESO-1, GPR20, Ly6k, OR51E2, TARP, GFR $\alpha$ 4, or a peptide of any of these antigens presented on MHC. In an embodiment, the first antigen is BCMA and the second antigen is CD19.

In an embodiment, the first CAR is encoded by a first nucleic acid sequence. In an embodiment, the second CAR is encoded by a second nucleic acid sequence. In an embodiment, the first and second nucleic acid sequences are disposed on a single nucleic acid molecule. In an embodiment, the first and second nucleic acid sequences are disposed on separate nucleic acid molecules. In an embodiment, the nucleic acid molecule or nucleic acid molecules are DNA or RNA molecules. In embodiments, the first and second nucleic acid sequences are situated in the same orientation, e.g., transcription of the first and second nucleic acid sequences proceeds in the same direction. In embodiments, the first and second nucleic acid sequences are situated in different orientations. In embodiments, a single promoter controls expression of the first and second nucleic acid sequences. In embodiments, a nucleic acid encoding a protease cleavage site (such as a T2A, P2A, E2A, or F2A cleavage site) is situated between the first and second nucleic acid sequences. In embodiments, the protease cleavage site is placed such that a cell can express a fusion protein comprising the first CAR and the second CAR and the fusion protein is subsequently processed into two peptides by proteolytic cleavage. In some embodiments, the first nucleic acid sequence is upstream of the second nucleic acid sequence, or the second nucleic acid sequence is upstream of the first nucleic acid sequence. In embodiments, a first promoter controls expression of the first nucleic acid sequence and a second promoter controls expression of the second nucleic acid sequence. In embodiments, the nucleic

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acid molecule is a plasmid. In embodiments, the nucleic acid molecule comprises a viral packaging element. In embodiments, the immune cell may comprise a protease (e.g., endogenous or exogenous protease) that cleaves a T2A, P2A, E2A, or F2A cleavage site.

In an embodiment, the first CAR comprises a first antigen-binding domain and the second CAR comprises a second antigen-binding domain. In an embodiment, the first or second antigen binding domain comprises a CDR, a VH, a VL, or a scFv disclosed herein, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto. In an embodiment, the first or second antigen binding domain comprises a CDR, a VH, a VL, or a scFv of an anti-BCMA antigen binding domain disclosed herein (e.g., an amino acid sequence disclosed in Tables 3-15, 19, 20, 22, and 26, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto). In an embodiment, the first or second antigen binding domain comprises a CDR, a VH, a VL, or a scFv of an anti-CD19 antigen binding domain disclosed herein (e.g., an amino acid sequence disclosed in Tables 2, 19, and 22, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto).

In an embodiment, the first antigen is BCMA and the second antigen is CD19. In an embodiment, an immune cell (e.g., a T cell or NK cell) expresses an anti-BCMA CAR, e.g., an anti-BCMA CAR described herein and an anti-CD19 CAR, e.g., an anti-CD19 CAR described herein. In an embodiment, the immune cell (e.g., a T cell or NK cell) comprises a first nucleic acid sequence encoding an anti-BCMA CAR, e.g., an anti-BCMA CAR described herein and a second nucleic acid sequence encoding an anti-CD19 CAR, e.g., an anti-CD19 CAR described herein. Table 19 shows exemplary amino acid and nucleic acid sequences of dual CAR constructs.

TABLE 19

TABLE 19-continued

TABLE 19-continued

TABLE 19-continued

TABLE 19-continued

Exemplary BCMA/CD19 dual CAR constructs and components thereof  
Dual BCMA/CD19 constructs

Identification	Protein sequence	DNA sequence (5'-3')
P161-P2A-duCD19.1		ctggccttgcgtgtccacgcgcggcaggccggaaat tgtatgaccagtcacccggcacttttagctt caccgggtgagcgcgaacccgttgcagagcc tcccaagacatctaaaatacttaatttggtatca acagaagccggacaggcttcgccttgcgtatct accacaccagccggctccatttgcgaatccctgc aggttacgggttagcgatctgggaccgactacac cctcaactatcagtcactgcagccagaggacttc ctgtctattttgtcagcaaggaaacaccctgc tacacccggacaggccacaaggctcgagatatt aggtggagggtgcagcggagggtgggtccggcg gtggaggaaggccagggtccaacttcaagaaagcc ccgggtttgtgaagccatcagaacttcttact gacttgtactgtgagcggagtgtctcccgatt acgggggttcttgcgttgcacggccaccggggaaag ggtctggatggattggagtgtattttgggtcttgc gactacttactaccaatcatccctcaagtacgc tcacccatctcaaggacaacttcaaaatcgatct tcactgtaaactgtcatctgtgaccgcggacac cgccgtgtacttgcgttgcacggatattatgc gccccggatctgcgttgcacggatctggggacagg actctgttacccgtgtccagcaccacgcgcgc gcccgcaccaccaacaccggccaccatgc cgccgttccctgtccctgcgcggccaggccgtgc ccaggccggggggccgcagtgacacgggggct ggacttcgcctgtatctacatctggcgccct tggccggactgtgtgggtcttcctgtact gttatcaccccttactgcacaaaggccagaaagaa actcctgtatataattcaaaaccattatgagac cagtcacaaactactcaagaggaaatggctgt tgcgttgcatttcagaagaagaaggaggatgt actggagatgttgcacggaggccgcgcgc ccgcgttaccaggccaggatctataac gagtcacatctaggacgaagaggactatgc tttggacaagagacgtggccggaccatgc ggggaaaggccgcagaaggaaaccctcaggaaagg ctgtacatgttgcacaaaggatgtggcc ggggggccaggccgcacgtggcccttaccagg ctcagtcacccgcaccaaggacaccatgc tcacatgcaggccctgccttcgc (SEQ ID NO: 215)

TABLE 19-continued

**Exemplary BCMA/CD19 dual CAR constructs and components thereof**  
**Dual BCMA/CD19 constructs**

Identification	Protein sequence	DNA sequence (5'-3')
R1B6 - P2A- duCD19.1		TCGVLLLSLVITLYCGRGRKKLLYIF aggagagaaggccggctcgcaactcgccgtgaaatc KQPFMRPVQTQQEEDGCSRFPPEEE agccgcacgcagatgtccagcttaccacgcagg GGCELRLVKFSRSADAPAYQQQNQLY gcagaaccagctctacaacgaactcaatcttggt NELNLGRREYYDVLKRRGRDPEMGG ggagagaggactacgactgtcgacacgcggaga KPRRKNPQEGLYNELQDKDMAEAYSE ggacggggccccaggaaaggccggaaaggccgg IGMKGERRRKGHDGLYQGLSTATKD aaagaatccccaaaggggcctgtacaacgagtc TYDALHMQALPPR (SEQ ID NO: 216) aaaaggataagatggcagaagcctatagcgagat ggtatgaaaggaaacgcagaagaggcaaggcca cgacggactgtaccaggactcgcacgcggccaca aggacacctatgacgccttcatatcgccggc ccgcctcgaaaagcgagactactaactcagct <u>gctgaagcaggctggagacgtggaggagaaccctg</u> <u>gacctatggccttaccagtgaccgcctgtctcg</u> <u>ccgctggcttgcgtcctacgcgcggccggc</u> aattgtatgaccgcgtcacccgcacttttagcc ttcacccggtagcgcgcacccctgtcttcgaga gcctccaaagacttcaaataacttattgtta tcaacagaagccggacaggcttcgcctgt tctaccacacccaggccgtccatctggaaatcc gccaggttcagcggtageggatctgggaccgacta caccctcaactatcagctactgcgcggaggact tegctgttatttcgtcagcaaggaaaccctgt ccctacacccttggacaggccaccaactgt taaagggtggaggtggcagccggaggaggtggcc gcccgtggaggaagccagggtccaaactccaaagg ggaccgggtcttgcgtgaaaccatcagaacactttt actgacttgtactgtgagcggagtgtcttcccg attacgggggtcttggatcagacgcacccgggg aagggtcttggatggattggagtgttggggc tgagactacttaccaatcatccctcaactgc ggttcacccatctaaaggacaactctaagatca gtgtcaacttgcattgtgcacccgcgg caccgcgtgtactattgcgtcaagcatactatt atggcgggagactcgcataatggattactgggg ggtactctggtccatgcgcggccacccgc agccgcgcgacccaaacccggccaccatcg cgtcgcagccccgtccctgcgcggcaggccgtgc cgcccaaggccggggggggcgcgtgcacacgg gtggacttcgcgttgcgtatcatatcttcc cttggccggactgtggggcttcttccgttca ctgggttatcaccccttacttgcacacgggg gaaactccgtatatatccaaacaaccattatga gaccgttacaaactactcaagaggaaatggctgt agtcggcgttccagaagaagaaggaggat tgaacttgcggatgttgcacccggccaccc cccccggttaccaggccaggccagaaccatctat aacggacttcaatcttggacgcggaggat tgttttggacaaggactgtggccggggaccctt tggggggaaagccggagaaggaaaccctt ggcctgtacaatgacttcgacaaagataatggc ggaggccatcactgtggatggatgggg gcccggggcaatggggcactgtggccctt gttctcaatgcaggccctggccctcgc ccttcacatgcaggccctggccctcgc (SEQ ID NO: 217)
MALPYTALLPLALLLHAARPEVQLI		ESGGGLVQPFGSRLSCAASGFTSS ggctcttcgtccacgcggctcgccggaaatgc YAMSVRQAPGKGLEWVSAISGSGGS agttgtcgaggactcaggccggaggacttgggtgcacccc TYYADSVKGRFTISDRNSKNLTLYLQM ggaggactcgtccgtcgactgtcgccgcacccctcagg NSLRAEDTAVYYCARRETVWVDPVSYN ctttaccccttccctcaatccatgttccctgt FDYWGQGTLVTVSSGGGGSGGGGGGG qacaggctcccggaaggacttgcgttgggtgtcc GGSGGGSDIQMTQSPPSSLASVGDR gccattagcggttccggccggaaaggacttactatgc VTITCRASQSISSYLNWYQQPKGPKAP cgactctgtgaaggccggcttcaactatcccccgg KLLIYAASSLQLSGGVPSRFSGSGSTD acaacttcaagaacaccatgttccatcaat FTLTISSLQPEDFATYVQSYSTPL tccctgaggccggcaatgcgggttactatgc TFGQGTKEVIEKTTTAPRPPTPAPTI cgtagacggggagtggtggccctacgcgttgc ASQPISLRPEACRPAAGGAHVTRGLD ggtacttgcactactggggacggccactctcg FACDIYIWAPLAGTCGVLLSLVITL actgtgtccctccgggtggatgggggggtgg YCKGRKKLLYIFKQPFMRPVQTTEE tggttcggccggaggatctgggggggggg EDGCSCRFPPEEEGGCELRLVKFSRSA cggacattcaatgacttcgttccctcc DAPAYQQQNOLYNEELNLGRREYYDV tccgcctccgtggggatcgcgttgc LDKRRGRDPEMGGKPRRKNPQEGLYN cggccggccaggacttgcgttgc ELQKDKMAEAYSEIGMKGERRRKGKH ctgtatcaccggccaggacttgcgttgc DGLYQGLSTATKTDYDALHMQALPPR ctgtatcaccggccaggacttgcgttgc

TABLE 19-continued

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 Exemplary BCMA/CD19 dual CAR constructs and components thereof  


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 Dual BCMA/CD19 constructs

Identification	Protein sequence	DNA sequence (5'-3')
GSGATNFSLLKQAGDVEENPGPMALP VTALLFLALLLHAARPEIVMTQSPA TLSLSPGERATLSCRASQDISKYLNW YQQKPGQAPRLLIYHTSRLHSGIPAR FSGSGSCTDYTLTISSLQPEDFAVYF CQQGNTLPYTFQGQTKLEIKGGGGSG GGGSGGGSQVQLQESQGPLVKPSET LSLTCTVSGVSLPDYGVSWIRQPPGK GLEWIGVIWGETTYYQSSLKSRVII SKDNSKNQVSLKLSSVTAADTAVYYC AKHYYYGGSYAMDYWGQGTIVVSST TPAPRPRPTPAPIASQPLSLRPEAC RPAAGGAHVTRGLDFACDIYIWAPLA GTCGVLLLSLVITLYCKRGRKKLLYI FKQPFMRRPVQTTQEEEDGCSRFPEEE EGGCCELRVKFPSRADAPAYCRQPNQL YNELNLGRREEEYDVLDKRRGRDPMEG GKPRRNPKQEGLYNELQDKMAEAAYS EIGMKGERRRGKHGDGLYQGLSTATK DTYDALHMQALPPR (SEQ ID NO: 218)	ccttcacgggttcgggatcgggctcaggcaccg acttcaccctgaccattagcgcctgcagccgg TSLSPGERATLSCRASQDISKYLNW YQQKPGQAPRLLIYHTSRLHSGIPAR FSGSGSCTDYTLTISSLQPEDFAVYF CQQGNTLPYTFQGQTKLEIKGGGGSG GGGSGGGSQVQLQESQGPLVKPSET LSLTCTVSGVSLPDYGVSWIRQPPGK GLEWIGVIWGETTYYQSSLKSRVII SKDNSKNQVSLKLSSVTAADTAVYYC AKHYYYGGSYAMDYWGQGTIVVSST TPAPRPRPTPAPIASQPLSLRPEAC RPAAGGAHVTRGLDFACDIYIWAPLA GTCGVLLLSLVITLYCKRGRKKLLYI FKQPFMRRPVQTTQEEEDGCSRFPEEE EGGCCELRVKFPSRADAPAYCRQPNQL YNELNLGRREEEYDVLDKRRGRDPMEG GKPRRNPKQEGLYNELQDKMAEAAYS EIGMKGERRRGKHGDGLYQGLSTATK DTYDALHMQALPPR (SEQ ID NO: 218)	GSGATNFSLLKQAGDVEENPGPMALP VTALLFLALLLHAARPEIVMTQSPA TLSLSPGERATLSCRASQDISKYLNW YQQKPGQAPRLLIYHTSRLHSGIPAR FSGSGSCTDYTLTISSLQPEDFAVYF CQQGNTLPYTFQGQTKLEIKGGGGSG GGGSGGGSQVQLQESQGPLVKPSET LSLTCTVSGVSLPDYGVSWIRQPPGK GLEWIGVIWGETTYYQSSLKSRVII SKDNSKNQVSLKLSSVTAADTAVYYC AKHYYYGGSYAMDYWGQGTIVVSST TPAPRPRPTPAPIASQPLSLRPEAC RPAAGGAHVTRGLDFACDIYIWAPLA GTCGVLLLSLVITLYCKRGRKKLLYI FKQPFMRRPVQTTQEEEDGCSRFPEEE EGGCCELRVKFPSRADAPAYCRQPNQL YNELNLGRREEEYDVLDKRRGRDPMEG GKPRRNPKQEGLYNELQDKMAEAAYS EIGMKGERRRGKHGDGLYQGLSTATK DTYDALHMQALPPR (SEQ ID NO: 218)
duBCMA .4 - P2A- duCD19 .1	MALPVTLALLPLALLLHAARPEVQLV ESGGGLVQPGGSLRLSCAVSGFALSN HGMWSVRRAPGKGLEWSVSGIVYSGST YYAASVKGRTIISRDNSRNTLYLQMN SLRPDETAIYYCSAHGGEVDVGQGT TVTVSSASGGGGGGGGGGSDIQ	atggccctccctgtcacccgcctgtgttccgc ggctcttcgtccacccgcgtcgccgcgaagtgc ggaggatcgctgagactgtcatgtgccgtgtccgg tttgccctgtccatggggatcgacccgcgtcgccgc gttttcccggtgagcgccacccgtgttgc agacccctcaagacatctaaaatacttaattt gtatcaacagaagccccgacaggcttcgccttc tgatctaccacaccagccggccatcttgaaatc ctggccagggttacgggttacggatctgggaccga ctacaccctcaatcagctactgcagccagg acttcgtgttatattctgtcagcaaggaaacacc ctggccatacccttggacaggccaccaagtcga gattaaagggtggagggtggcagcggggagggtgg ccggcggtggaggaaaggccaggccaactccaaagaa agccggaccgggtcttgcagccatcagaaactct tttactgtactgtactgtgacggagtgcttc ccgatatacggtgtttggatcagacaggccaccc ggaaagggttctggatggattggagtgttgggg ctctgagactacttaccaatcatccctcaagt caccgcgtcaccatctaaggacaactctaagaat cagggtgtcactgaaactgtcatctgtgaccgc cgacaccgcgtgtactattgcgttaaggattact attatggcgaggactcgcaatggattactgggg cagggtactctgtcacccgtgtccaggccaccc gcacccgcgcgcaccaccaacccggcccccacca tcgcgtcgcacccctgtccctgcgcggccagg tgccggccagccggggggggccgtgcacaccc ggggctggacttcgcctgtgatatctacatctgg cgcccttggccgggacttgggggtcttctctg tcaactgtttatcaccccttactgtcaaacgggg aaagaaaactctgttatataattcaaacaaccat tgagaccaggataaaactactcaagaggaaatggc tgttagctggcgattttccagaagaaggaaaggagg atgtgaactgtggactgtggatgttgcaggagg acggcccccgcgttacccgcaggccaggccact tataacgcgtcaatctaggacgaagaggagg cgatgtttggacaaggagacgtggggggggccct agatggggggaaaggccgagaaggaaacccctc gaaggcctgtacaatgaaactgcagaaaatagaat ggcggaggccataggatggatggatggaaagg agccggccggggggcaaggggcacgtggcccttac cagggtctcagtgacccaccaaggacaccc cgcccttcacatgcaggccctgcggccctcgc (SEQ ID NO: 219)

duBCMA .4 -  
P2A-  
duCD19 .1

MALPVTLALLPLALLLHAARPEVQLV  
ESGGGLVQPGGSLRLSCAVSGFALSN  
HGMWSVRRAPGKGLEWSVSGIVYSGST  
YYAASVKGRTIISRDNSRNTLYLQMN  
SLRPDETAIYYCSAHGGEVDVGQGT  
TVTVSSASGGGGGGGGGGSDIQ

TABLE 19-continued

TABLE 19-continued

Exemplary BCMA/CD19 dual CAR constructs and components thereof  
Dual BCMA/CD19 constructs

Identification	Protein sequence	DNA sequence (5'-3')
duCD19.1- P2A- duBCMA .4	MALPV TALLPL ALLL HAAR PEIV M T atggc tt acc agt gac gg ctt tg t ctg ccc ct QSPATL SLPGERATL SCRAS QDISK ggc tt gt gtc acg cgc ccagg cgg gaa att g YLNW YQQK PGPQ APRLLI YHTS RLHSG tga tgg ccc agt cacc ggc cact tta gct ttc a IPAR FSGSGSGT DYT LTI SS LQP EDF ccc gg tga g cgc ca acc ctg t ctg cag a g ctc AVYFC CQGNTL PYTF GQGT KLEIKGG cca a gac at ct caaa ta ac tt aatt gg t at caa c GGSGGGGS GGGS QVQL QESGP GLVK aya agg ccc gg agc ggt ct cgc t ct gat ct ac PSET LSLT CT VSG VSL EDYGV SWIRQ cacca cgg cgc t catt ct gga at cc tt gcc ga PPG KGLE WIG VIWG SETT YYQSS LKS gtt cag cgg tage gga t ct gg a ccc gact a cacc RTVI SKDN SKN QVSL KLSS VTA DTA tc aact at ca gtc a ct gca gcc a gagg a ct cgt VYV CAKHY YYGGGS YMD YWGGT LVT gtc tattt ctg tca ggg a ccc ac tt ccc gcca VSSTT PAPR PT PAP TIAS QPLS RSL cacc ttt gg a ccc ggg a cca a gtc cag aatt aa PEACR PAAGGA VHT RGL DFACD IYIW gtt gag ggt gg cag cgg a ggg a ggt tgg tcc ggg APLAGT CGV LLSL SVIT LYCK RGR KK gg a gga a ggc a ggt tca a ct cca a gga a ccc LLY FQKF PMRP VQT QEE GCSC RF ggg tct tgg tga a ggc a ctt a ggg a a ctt PEEE GGC ELR VFK FSRS ADAPAY QQQ gtt gtc t a ct ggg a ggt tgg tct ccc ctt a QNQL YNL NL GR REE YD VL D KRR GRD ggg g tct tgg at c a g a c a g c a c c g g g PEM GKP PRK N P QEG LYNE L QDK MA tct gg a at gg a t t g g a g t a t t t g g g EAY SEI GM KGERR R GKH D GLY QGLS ct a ct a ct a ca a t ccc t ca a gtc a c c g TAK DTY DAL HMQ AL PPR GS ATNF S acc a t cta a a g g a a c a c t a g g a t LLK QAG DV EEN PGPM AL PV TALLPL a ct ggg a a c t g t a c t t g a c c g c a g LLL HAAR PEV QLV ESG GGL VQPGGS c cg t g t a c t a t t g c g t a a g c a t t a c t LRL SC AVS GF QNL NHG MS VWR RA PGK ggg a g g t a c g c a t t g g a t t c GLEW VSG I VY SG STT Y AAS VKG RFT I T ctt g t c a c c t g t c a c c a g SRD NSR NT L YQ MN S L R P E D T A I Y Y C c c g c a c c a a c a c c SAH GGE SD V W QG QT TV T VSS AS GGGG c a g c c c t g t c c t g c g SGGG S GGG SD I QL T QSP S L SASV a g c g c g c g g g g g c a g c g GDR VTI CRAS Q SI SS YLNW Y QQK PG act t c g c t g t g a t a t c a c t KAP KLLI YIA ASS L QSG VPS RFS GSGS g c c g g a c t g t g g g GTD FTL TISS L QP E D F A T Y Y C Q S Y S t a t c a c c t t a c t PTY TF GG Q GT KVE I KTTT PAPR PPTA tcc t g t a t a t c a a c a c PTIAS QPLS LR PEA CRPA AGGA VHTR gta a a a c t a c t a a g g a a g GLDF AC D IYI WA PLAGT CGV L L S L V c c g a t t c c a a g a a g IT LYC KRG R K L L YI FK QP FM RP VQT tg a g a g t a g t t c a g TQE EDGCS CRF PEE E EGG C E L R V K F S g c g t a c c a c RSADAPAY Q QG QNOL YN E L N L G R REE g t c a a c t a g g a c YD VL DK RR GRD P E M G K P R R K N P Q E G t g g a a q a g LYN E L QDK MA E AY SEI GM KGERR RG g g a a g c c g a KGHD GLY QGL S T A K D T Y D A L H M Q A L g t a a c t g a a c PPR (SEQ ID NO: 222)	atggcggaggcctacagtggatggatggaaaggcg cgagccggaggggcaaggggcacatggcccttgc accagggttcagtacagccacaaggacacatcc gaccccttccatgcggccctggccctgc (SEQ ID NO: 221)

TABLE 19-continued

TABLE 19-continued

Exemplary BCMA/CD19 dual CAR constructs and components thereof Dual BCMA/CD19 constructs	
Identification	Protein sequence
	DNA sequence (5'-3')
	SRSADAPAYQQGQNOLYNELNLGRRE EYDVLDKRRGRDPEMGGKPRRKNPQE GLYNELQDKDMAEAYS EIGMKGERRR GKGHDGLYQQLSTATKDTYDALHMQA LPPRGSGATNFSLLKQAGDVEENPG (SEQ ID NO: 226) Anti-CD19 CAR arm: EIVMTQSPATLSLSPGERATLSCRAS QDISKYLNWYQQKPGQAPRLLIYHTS RLHSGIPARFSGSGSGTDXTLTISSL QPEDFAVYFCQQGNTLPYTFQGQGTKL EIKGGGGSGGGGGGGSQVQLQESG PGLVKPSETLSLTCTVSGVSLPDYGV SWIRQPPGKGLEWIGVIWGSETTYQ SSLKSRVTISKDNSKNQVSLKLSSVT AADTAVYYCAKHYYYYGGSYAMDYWGQ GTLTVSSTTTPAPRPTPAFTIASQ PLSLRPEACRPAAAGGAHVTRGLDFAC DIYIWAPLAGTCGVLLSLVITLYCK RGRKKLLYIFKQPFMRPVQTTQEEEDG CSCRFPEEEEGGCERVKFSRSADAP AYQQGQNOLYNELNLGRREEYDVLDK RGRDPPEMGGKPRRKNPQEGLYNELQ KDKDMAEAYS EIGMKGERRRGKGHDGL YQGLSTATKDTYDALHMQALPPR (SEQ ID NO: 225)
Predicted resultant proteins from R1B6-P2A-duCD19.1	Anti-BCMA CAR arm: EVQLLESGGGLVQPGGSLRLSCAASG FTFSSYAMSWSVRQAPGKGLEWVSAIS GSGGSTYYADSVKGRFTISRDN SKNT LYLQMNSLRAEDTAVYYCARREWVPY DVSWYFDYWGQGTLTVSSGGGGSGG GGSGGGGGGGSDIMQTQSPSSLSA SVGDRVTITCRASQSISYYLNWYQQK PGKAPKLLIYIASSLQSGVPSRFSGS GSGTDFTLTISLQPEDFATYYCQQS YSTPLTFQGQGTKVEIKTTTPAPRPT PAPTIASQPLSLRPEACRPAAAGGAHV TRGLDFACDIYIWAPLAGTCGVLLSL LVITLYCKRGRKKLLYIFKQPFMRPV OTTQEEEDGCSRFPEEEEGGCERVK FSRSADAPAYQQGQNOLYNELNLGR EYDVLDKRRGRDPEMGGKPRRKNPQ EGLYNELQDKDMAEAYS EIGMKGER RGKGHDGLYQQLSTATKDTYDALHMQ ALPPRGSGATNFSLLKQAGDVEENPG (SEQ ID NO: 227) Anti-CD19 CAR arm: EIVMTQSPATLSLSPGERATLSCRAS QDISKYLNWYQQKPGQAPRLLIYHTS RLHSGIPARFSGSGSGTDXTLTISSL QPEDFAVYFCQQGNTLPYTFQGQGTKL EIKGGGGGGGGGGGGSQVQLQESG PGLVKPSETLSLTCTVSGVSLPDYGV SWIRQPPGKGLEWIGVIWGSETTYQ SSLKSRVTISKDNSKNQVSLKLSSVT AADTAVYYCAKHYYYYGGSYAMDYWGQ GTLTVSSTTTPAPRPTPAFTIASQ PLSLRPEACRPAAAGGAHVTRGLDFAC DIYIWAPLAGTCGVLLSLVITLYCK RGRKKLLYIFKQPFMRPVQTTQEEEDG CSCRFPEEEEGGCERVKFSRSADAP AYQQGQNOLYNELNLGRREEYDVLDK RGRDPPEMGGKPRRKNPQEGLYNELQ KDKDMAEAYS EIGMKGERRRGKGHDGL YQGLSTATKDTYDALHMQALPPR (SEQ ID NO: 225)
Predicted resultant proteins from duBCMA.4-P2A-duCD19.1	Anti-BCMA CAR arm: EVQLVESGGGLVQPGGSLRLSCAVSG FALSNHGMSWVRRAPGKGLEWVSGIV YSGSTYYAASVKGRTISRDN SRNTL YLQMNSLRPEDTAIYYCSAHGGESDV WGQGTTVTVSSASGGGGGGGGGGGG

TABLE 19-continued

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 Exemplary BCMA/CD19 dual CAR constructs and components thereof  


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 Dual BCMA/CD19 constructs

Identification	Protein sequence	DNA sequence (5'-3')
	GSDIQLTQSPSSLSASVGDRVTITCR ASQSISYYLNWYQQKPGKAPKLLIYA ASSLQSGVPSRSGSGSGTDFTLTIS SLQPEDFATYYCQQSYSTPYTFGQGT KVEIKTTTPAPRPPPTPAPTIASQPLS LRPEACRPAAGGAHVTRGLDFACDIY IWAPLAGTCGVLLLSLVITLYCKRGR KKLLYIFKQPFMRPVQTTQEEEDGCSC RFPEEEEGGCELRVKFSRSADAPAYQ QGQNQLYNELNLGRREEYDVLDKRRG RDPEMGGKPRRKNPQEGLYNELQDK MAEAYSEIGMKGERRRGKGHDGLYQG LSTATKDTYDALHMQALPPRGSGAIN FSLLKQAGDVEENPG (SEQ ID NO: 228) Anti-CD19 CAR arm: EIVMTQSPATLSLSPGERATLSCRAS QDISKYLNWYQQKPGQAPRLLIYHTS RLHSGIPARFSGSGSGTDXTLTISSL QPEDFAVYFCQGNTLPYTFGQGTKL EIKGGGGGGGGGGGGGGSQVQLQESG PGLVKPSETLSLTCTVSGVSLPDYGV SWIRQPGKGLEWIGVIWGSETTYQ SSLKSRVTISKDNNSKNQVSLKLSSVT AADTAVVYCAKHYGGSYAMDYWGQ GTLTVSSTTPAPRPPPTPAPTIASQ PLSLRPBACRPAAGGAHVTRGLDFAC DIYIWAPLAGTCGVLLSLVITLYCK RGRKKLLYIFKQPFMRPVQTTQEEEDG CSCRFPEEEEGGCELRVKFSRSADAP AYQQGQNQLYNELNLGRREEYDVLDK RRGRDPEMGGKPRRKNPQEGLYNELQ KDKMAEAYSEIGMKGERRRGKGHDGL YQGLSTATKDTYDALHMQALPPR (SEQ ID NO: 225)	
Predicted resultant proteins from duCD19.1- P2A- duBCMA.4	Anti-CD19 CAR arm: EIVMTQSPATLSLSPGERATLSCRAS QDI SKY- LNWYQQKPGQAPRLLIYHTS RLHSGIPARFSGSGSGTDXTLTISSL QPEDFAVYFCQGNTLPYTFGQGTKL EIKGGGGGGGGGGGGGGSQVQLQESG PGLVKPSETLSLTCTVSGVSLPDYGV SWIRQPGKGLEWIGVIWGSETTYQ SSLKSRVTISKDNNSKNQVSLKLSSVT AADTAVVYCAKHYGGSYAMDYWGQ GTLTVSSTTPAPRPPPTPAPTIASQ PLSLRPBACRPAAGGAHVTRGLDFAC DIYIWAPLAGTCGVLLSLVITLYCK RGRKKLLYIFKQPFMRPVQTTQEEEDG CSCRFPEEEEGGCELRVKFSRSADAP AYQQGQNQLYNELNLGRREEYDVLDK RRGRDPEMGGKPRRKNPQEGLYNELQ KDKMAEAYSEIGMKGERRRGKGHDGL YQGLSTATKDTYDALHMQALPPRGS ATNFSLLKQAGDVEENPG (SEQ ID NO: 229) Anti-BCMA CAR arm: EVQLVESGGGLVQPGGSLRLSCAVSG FALSNHGMSWRRRAPGKGLEWVSGIV YSGSTYYAASVKGRFTISRDNSRNTL YLQMNSLRPEDTAIYYCSAHGGESDV WQQGTTTVSSASGGGGGGGGGGGG GSDIQLTQSPSSLSASVGDRVTITCR ASQSISYYLNWYQQKPGKAPKLLIYA ASSLQSGVPSRSGSGSGTDFTLTIS SLQPEDFATYYCQQSYSTPYTFGQGT KVEIKTTTPAPRPPPTPAPTIASQPLS LRPEACRPAAGGAHVTRGLDFACDIY IWAPLAGTCGVLLSLVITLYCKRGR KKLLYIFKQPFMRPVQTTQEEEDGCSC RFPEEEEGGCELRVKFSRSADAPAYQ QGQNQLYNELNLGRREEYDVLDKRRG RDPEMGGKPRRKNPQEGLYNELQDK	

TABLE 19-continued

Exemplary BCMA/CD19 dual CAR constructs and components thereof		
Dual BCMA/CD19 constructs		
Identification	Protein sequence	DNA sequence (5'-3')
	MAEAYSEIGMKGERRRGKGHDGLYQG LSTATKDTYDALHMQALPPR (SEQ ID NO: 230)	

TABLE 22

Amino acid sequences of exemplary components of dual CARs			
SEQ ID NO	Name/Description	Sequence	
<u>PI61</u>			
SEQ ID NO: 86	HCDR1 (Kabat)	SYGMH	
SEQ ID NO: 87	HCDR2 (Kabat)	VISYDGSNKYYADSVKG	
SEQ ID NO: 88	HCDR3 (Kabat)	SGYALHDDYYGLDV	
SEQ ID NO: 47	HCDR1 (Chothia)	GFTFSSY	
SEQ ID NO: 89	HCDR2 (Chothia)	SYDGSN	
SEQ ID NO: 88	HCDR3 (Chothia)	SGYALHDDYYGLDV	
SEQ ID NO: 90	HCDR1 (IMGT)	GFTFSSYG	
SEQ ID NO: 91	HCDR2 (IMGT)	ISYDGSNK	
SEQ ID NO: 92	HCDR3 (IMGT)	GGSGYALHDDYYGLDV	
SEQ ID NO: 93	VH	QVQLQESGGGVVQPGRLSLRLSCAASGFTFSSYGMHWVRQAPGKLEWV AVISYDGSNKYYADSVKGRFTISRDNISKNTLYLQMNSLRAEDTAVYYCG GSGYALHDDYYGLDVWGQGTIVTVSS	
SEQ ID NO: 94	DNA VH	CAAGTCAGCTGCAGGAATCCGGTGGCGGAGTCGTGCAGCCTGGAAAG GAGCCTGAGACTCTCATGCGCCGCGTCAGGGTCACCTTTCTCCCTAC GGGATGCATTGGGTCAAGACAGCCCCGGAAAGGGACTCGAATGGGT GGCTGTGATCAGCTACGACGGCTCCAACAAGTACTACGCCACTCGT GAAAGGCCGGTTCACTATCTCCGGGACAACTCAAGAACACGGCTGTA TCTGCAATGAATTCACTGCGCGCGGAGGATACCGCTGTACTACTG CGGTGGGCTCGGGTACGCCCTGCACGATGACTATTACGGCCTTGACGT CTGGGGCCAGGGAACCCCTCGTGAATGTGTCAGC	
SEQ ID NO: 95	LCDR1 (Kabat)	TGTSSDVGGNYVS	
SEQ ID NO: 96	LCDR2 (Kabat)	DVSNRPS	
SEQ ID NO: 97	LCDR3 (Kabat)	SSYTSSSTLYV	
SEQ ID NO: 98	LCDR1 (Chothia)	TSSDVGGNY	
SEQ ID NO: 99	LCDR2 (Chothia)	DVS	

TABLE 22-continued

<u>Amino acid sequences of exemplary components of dual CARs</u>		
SEQ ID NO	Name/ Description	Sequence
SEQ ID NO: 100	LCDR3 (Chothia)	YTSSSTLY
SEQ ID NO: 101	LCDR1 (IMGT)	SSDVGGYNY
SEQ ID NO: 99	LCDR2 (IMGT)	DVS
SEQ ID NO: 97	LCDR3 (IMGT)	SSYTSSSTLYV
SEQ ID NO: 102	VL	QSALTOPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQOHPGKAPKLMIVDVSNRPSGSNSKGNTASLTISGLQAEDEADYYCSSLTSSSTLYVFGSGTKVTVL
SEQ ID NO: 103	DNA VL	CAGAGCGCACTGACTCAGCCGGCATCCGTGTCGGTAGCCCCGGACAGTCGATTACCATCTCCTGTACCGGCACCTCCCTCGACGTGGGAGGGTACAACTACGTGTCGGTACCGACAGCACCCAGGAAAGGCCCTAAGTTGATCTACGATGTGTCAAACCGCCGCTCGAGACTACTGCTCGAGCTACACATCCTCGCAAGCCGAGGATGAGCCGACTACTGCTCGAGCTACACATCCTCGAGCACCCGTGCTCGGGACTAAGGTACCCGTGCTG
SEQ ID NO: 104	Linker	GGGGSGGGGGGGGS
SEQ ID NO: 105	scFv (VH-linker-VL)	QVQLQESGGGVVQPGRLSLRLSCAASGFTFSSYGMHWVRQAPGKLEWVAVISYDGSNKYADSVKGRFTISRDNSKNLTLQMNLSRAEDTAVYYCGVSGYALHDDYYGLDWVGQGTLTVSSGGGGSGGGGGGGQSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQOHPGKAPKLMIVDVSNRPSGVSNRPSGSNSKGNTASLTISGLQAEDEADYYCSSLTSSSTLYVFGSGTKVTVL
SEQ ID NO: 106	DNA scFv	CAAGTCAGCTGCAGGAATCCGGTGGCGGAGTCGTGCAGCCTGGAAGGAGACTCTCATGCGCCGGCTCAGGGTCACTTTCCTCCTACGGATGCAATTGGGTGCGTGATCAGCTACGACGGCTCCAACAAGTAACGCGACTCCGTGAAAGGCCGTTCACTATCTCCGGACAACCCAAGAACACGCTGTAATCGTCAATGAAATTCACTGCGCCGGAGGATACCGCTGTACTACTCGCGTGGCTCCGGTTACCCCTGCACGATGACTATTACGGCCTTGACGTCTGGGGCAGGGAACCCCTCGTGACTGTGTCAGGAGGGGTGGATCGCAGAGCGCACTGACTCGGGCGAGGAGGATCAGGAGGGGGTGACGTGATTACCATTCCTGACCGCATCGTGTCCGGTACGCCCCGGACAGTCGATTACCATTCCTGTACCGGGCACCTCCCGACGTGGGGGTACAACTAAGTGTGCTGTTACAGCAGCACCAGGAAAGGCCCTAAGTTGATGATCTACGATGTGCAAACCGCCCCTGCTGGAGTCTCAACCGGTTCTCCGGCTCAAGTCGGGACTACTGCTCGAGCTACACATCCTCGAGCACCCCTACGTGTTACGGCTCGGGACTAAGGTACCCGTGCTG
<u>R1B6</u>		
SEQ ID NO: 44	HCDR1 (Kabat)	SYAMS
SEQ ID NO: 45	HCDR2 (Kabat)	AISGSGGSTYYADSVKG
SEQ ID NO: 46	HCDR3 (Kabat)	REWVPYDVSFYFDY
SEQ ID NO: 47	HCDR1 (Chothia)	GFTFSSY
SEQ ID NO: 48	HCDR2 (Chothia)	SGSGGS
SEQ ID NO: 46	HCDR3 (Chothia)	REWVPYDVSFYFDY
SEQ ID NO: 49	HCDR1 (IMGT)	GFTFSSYA

TABLE 22-continued

Amino acid sequences of exemplary components of dual CARs		
SEQ ID NO	Name/ Description	Sequence
SEQ ID NO: 50	HCDR2 (IMGT)	ISGGGGST
SEQ ID NO: 51	HCDR3 (IMGT)	ARREWVPYDVSWYFDY
SEQ ID NO: 52	VH	EVOLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKLEWVS AISGGGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARR EWVPYDVSWYFDYWGQGTIVTVSS
SEQ ID NO: 53	DNA VH	GAAGTGCAGTTGCTGGAGTCAGGCGGAGGACTGGTGCAGCCCGGAGG ATCGCTTCGCTTGAGCTGCGCAGCCTCAGGCTTACCTTCTCCTCTAC GCCATGTCTGGTCAGACAGGCTCCGGAAAGGACTGGAATGGGT GTCGCCATTAGCGGTTCCGGCGGAAGCACTTACTATGCCGACTCTGT GAAGGGCGCTTCACTATCTCCGGGACAACCTCAAGAACACCCGTGA TCTCCAAATGAATTCCCTGAGGGCGAAGATAACCGCGGTGTACTACTG CCTAGACGGGAGTGGGTGCCCTACGATGTCAGCTGGTACTTCGACTA CTGGGACAGGGCACTCTCGTACTGTGCTCC
SEQ ID NO: 54	LCDR1 (Kabat)	RASQSISSYLN
SEQ ID NO: 55	LCDR2 (Kabat)	AASSLQS
SEQ ID NO: 56	LCDR3 (Kabat)	QQSYSTPLT
SEQ ID NO: 57	LCDR1 (Chothia)	SQSISSY
SEQ ID NO: 58	LCDR2 (Chothia)	AAS
SEQ ID NO: 59	LCDR3 (Chothia)	SYSTPL
SEQ ID NO: 60	LCDR1 (IMGT)	QSISSY
SEQ ID NO: 58	LCDR2 (IMGT)	AAS
SEQ ID NO: 56	LCDR3 (IMGT)	QQSYSTPLT
SEQ ID NO: 61	VL	DIQMTQSPSSLSASVGDRVITICRASQSISSYLNWYQQKPGKAPKLLIYAA SSLQSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQSYS- TPLTFGQGTK VEIK
SEQ ID NO: 62	DNA VL	GACATTCAAATGACTCAGTCCCCGCTCTCCCTCTCCGCCCTCCGTGGAA GATCGCGTCACGATCACGTGCAAGGCCAGCCAGACATCTCCAGCTAC CTGAACGGTACAGCAGAACGCCAGGGAAAGGCAACGGACTCTGAT CTACGCCGCTAGCTCGCTGCAGTCGGCGTCCCTCACGGTCTCGGG ATCGGGCTCAGGACCCGACTTCACCCGTGACCAATTAGCAGCCTGCAGCC GGAGGACTTCGGACATACTACTGTCAAGCACTCATCTCCACCCCTCT GACCTTCGGCAAGGGACAAAGTGGAGATCAAG
SEQ ID NO: 63	Linker	GGGGSGGGGGSGGGGGSGGGGS
SEQ ID NO: 64	scFv (VH-linker-VL)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKLEWVS AISGGGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARR EWVPYDVSWYFDYWGQGTIVTVSSGGGGSGGGGGSGGGSDIQ MTQSPSSLSASVGDRVITICRASQSISSYLNWYQQKPGKAPKLLIYAASSL QSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQSYS- TPLTFGQGTKVEIK
SEQ ID NO: 65	DNA scFv	GAAGTGCAGTTGCTGGAGTCAGGCGGAGGACTGGTGCAGCCCGGAGG ATCGCTTCGCTTGAGCTGCGCAGCCTCAGGCTTACCTTCTCCTCTAC GCCATGTCTGGTCAGACAGGCTCCGGAAAGGACTGGAATGGGT GTCGCCATTAGCGGTTCCGGCGGAAGCACTTACTATGCCGACTCTGT GAAGGGCGCTTCACTATCTCCGGGACAACCTCAAGAACACCCGTGA

TABLE 22-continued

<u>Amino acid sequences of exemplary components of dual CARs</u>		
SEQ ID NO	Name/Description	Sequence
		TCTCCAAATGAATTCCCTGAGGGCCGAAGATAACCGCGGTACTACTG CGCTAGACGGGGAGTGGGTGCCCTACGATGTCACTGGTACTTCGACTA CTGGGGACAGGGCAGTCTCGTACTGTGTCTCCGGTGGTGGATC GGGGGGTGGTGGTTGGGGAGGAGATCGGAGGAGGGTGG ACATTCAAATGACTCAGTCCCCGTCTCCCTCTCCGCCTCGTGGAG ATCGCGTACAGTCAGTGCAAGGGCAGCCAGAGCATCTCCAGCTACC TGAACGTGACAGCAGAAGCCAGGGAAAGGCACCGAAGGTCTGATC TACGCCGCTAGGCTCGCTGCAGTCCGGGTCCCTCACGGTTCTCGGGA TCGGGCTCAGGCACCGACTTACCCCTGACCATATACCGCTGCAGCCG GAGGACTTCGCGACATACTACTGTCAGCAGTCATACTCCACCCCTTG ACCTTCGGCCAAGGGACAAAGTGGAGATCAAG
<u>R1G5</u>		
SEQ ID NO: 44	HCDR1 (Kabat)	SYAMS
SEQ ID NO: 45	HCDR2 (Kabat)	AISGSGGSTYYADSVKG
SEQ ID NO: 76	HCDR3 (Kabat)	REWWGESWLFDY
SEQ ID NO: 47	HCDR1 (Chothia)	GFTFSSY
SEQ ID NO: 48	HCDR2 (Chothia)	SGSGGS
SEQ ID NO: 76	HCDR3 (Chothia)	REWWGESWLFDY
SEQ ID NO: 49	HCDR1 (IMGT)	GFTFSSYA
SEQ ID NO: 50	HCDR2 (IMGT)	ISGSGGST
SEQ ID NO: 77	HCDR3 (IMGT)	ARREWWGESWLFDY
SEQ ID NO: 78	VH	EVQLESGGGLVQPQPGSRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS AISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARR EWWGESWLFDYWGQGLTVTSS
SEQ ID NO: 79	DNA VH	GAAGTGCAGTTGCTGGAGTCAGGCGGGAGGACTGGTGCAGCCCCGGAGG ATCGCTTCGCTTGAGCTGCGCAGCCTCAGGCTTACCTTCTCCCTAC GCCATGTCCTGGGTAGACAGGCTCCGGGAAGGGACTGGAAATGGGT GTCCGCCATTAGCGGTTCCGGCGGAAGCAGTACTATGCGGACTCTGT GAAGGGCGCTTCACTATCTCCGGGACAATCCAAGAACACCTGTGA TCTCCAAATGAATTCCCTGAGGGCCGAAGATAACCGCGGTACTACTG CGCTAGACGGGAGTGGTGGGGAGAAAGCTGGCTGTTGACTACTGGG GACAGGGCACTCTCGTACTGTGTCTCC
SEQ ID NO: 54	LCDR1 (Kabat)	RASQSISSYLN
SEQ ID NO: 55	LCDR2 (Kabat)	AASSLQS
SEQ ID NO: 56	LCDR3 (Kabat)	QQSYSTPLT
SEQ ID NO: 57	LCDR1 (Chothia)	SQSISSY
SEQ ID NO: 58	LCDR2 (Chothia)	AAS
SEQ ID NO: 59	LCDR3 (Chothia)	SYSTPL
SEQ ID NO: 60	LCDR1 (IMGT)	QSISYY

TABLE 22-continued

<u>Amino acid sequences of exemplary components of dual CARs</u>		
SEQ ID NO:	Name/ Description	Sequence
SEQ ID NO: 58	LCDR2 (IMGT)	AAS
SEQ ID NO: 56	LCDR3 (IMGT)	QQSYSTPLT
SEQ ID NO: 61	VL	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAA SSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYS- TPLTEFGQGTK VEIK
SEQ ID NO: 62	DNA VL	GACATTCAAATGACTCAGTCCCCGTCCTCCCTCTCCGCCCTCCGTGGGA GATCGCGTCACGGATCACGTGCAGGGCCAGCCAGACATCTCAGCTAC CTGAACGGTACCAAGCAGAAGCAGGGAAAGCACCGAACGCTCCTGAT CTACGGGCTCAGGCCACCGACTTCACCCCTGACCATTAGCAGCTGCAGCC GGAGGACTTCGGACATACTACTGTCAAGCAGTCATACTCCACCCCTCT GACCTTCGGCCAAGGGACCAAAAGTGGAGATCAAG
SEQ ID NO: 63	Linker	GGGGSGGGGSGGGGGGGGS
SEQ ID NO: 80	scFv (VH-linker-VL)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKLEWVS AISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARR EWWGESWLFDYWQGTLTVTSSGGGGGGGGGGGGGGGGSDIOMT QSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQS GVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSPLTFGQGTKVEIK
SEQ ID NO: 81	DNA scFv	GAAGTCAGTTGCTGGAGTCAGGCGGAGGACTGGTGCAGCCGGAGG ATCGCTTCGCTTGAGCTGCGCAGCCTCAGGCTTACCTTCTCCTAC GCCATGCTCCTGGGTCAAGACAGCTCCGGGAAGGGACTGGAATGGGT GTCCGCCATTAGCGGTTCCGGCGGAAGCAGTACTATGCGGACTCTGT GAAGGGCGCTTCACTATCTCCGGGACAATCCAAGAACACCCGTGA TCTCAAATGAATTCCCTGAGGGCGGAAGATAACCGCGGTGTACTACTG CGCTAGACGGAGGTGGTGGGGAGAAAGCTGGCTGTTCGACTACTGG GACAGGGCACTTCGTAAGTGTGCTCCGGTGGTGGATCGGGGG GTGGTGGTTCGGGCGGAGGAGATCTGGAGGGAGGGTCGGACATT CAAATGACTCAGTCCCCTGCTCCCTCTCCGCTCTGGAGATCGC GTACGATCACGTGAGGGCCAGCCAGAGCATCTCCAGCTACCTGAAC TGGTACCGAGCAAGCCAGGGAAAGGCACCGAACGCTCTGATCTACGC CGCTAGCTCGCTGCAGTCCGGCTCTTACGGTTCTCGGGATCGGG CTCAGGCACCGACTTCACCCCTGACCATTAGCAGCCTGCAGCCGGAGGA CTTCAGCGACATACTACTGTCAAGCAGTCATACTCCACCCCTCTGACCTTC GCCAAGGGACCAAAAGTGGAGATCAAG
<u>duBCM</u>		
<u>A.4</u>		
SEQ ID NO: 231	HCDR1 (Kabat)	NHGMS
SEQ ID NO: 232	HCDR2 (Kabat)	GIVYSGSTYYASVKG
SEQ ID NO: 233	HCDR3 (Kabat)	HGGESDV
SEQ ID NO: 234	HCDR1 (Chothia)	GFALSNH
SEQ ID NO: 235	HCDR2 (Chothia)	VYSGS
SEQ ID NO: 233	HCDR3 (Chothia)	HGGESDV
SEQ ID NO: 236	HCDR1 (IMGT)	GFALSNHG
SEQ ID NO: 237	HCDR2 (IMGT)	IVYSGST
SEQ ID NO: 238	HCDR3 (IMGT)	SAHGGESDV

TABLE 22-continued

Amino acid sequences of exemplary components of dual CARs			
SEQ ID NO:	Name/Description	Sequence	
SEQ ID NO: 239	VH	EVQLVESGGGLVQPGGSLRLSCAVSGFALS NHMSWVRAPGKGLEWV SGIVYSGSTYYAASVKGRTFISRDNSRNTLYLQMNSLRPEDTAI YYCSAHG GESDVWGQGTTTVSS	
SEQ ID NO: 262	DNA VH	GAAGTGCAATTGGTGGAAATCAGGGGGAGGACTTGTGCAGCCTGGAGG ATCGCTGAGACTGTATGTGCCGTGTCGGCTTTGCCCTGTCACCCAC GGGATGTCTGGTCCGCCGCGCCTGGAAAGGGCTCGAATGGGT GTCGGGTATTGTGTACAGCGTAGCACCTACTATGCCGATCCGTGAA GGGGAGATTCCATCAGCGGGACAACCTCAGGAACACTCTGTACCT CCAATGAATTGCGTAGGCCAGAGGACACTGCCATCTACTACTGCTC CGCGCATGGCGGAGACTCGACGCTGGGACAGGGGACCACCGTGA CCGTGTCTAGC	
SEQ ID NO: 54	LCDR1 (Kabat)	RASQSISSYLN	
SEQ ID NO: 55	LCDR2 (Kabat)	AASSLQS	
SEQ ID NO: 240	LCDR3 (Kabat)	QQSYSTPYT	
SEQ ID NO: 57	LCDR1 (Chothia)	SQSISYY	
SEQ ID NO: 58	LCDR2 (Chothia)	AAS	
SEQ ID NO: 241	LCDR3 (Chothia)	SYSTPY	
SEQ ID NO: 60	LCDR1 (IMGT)	QSISYY	
SEQ ID NO: 58	LCDR2 (IMGT)	AAS	
SEQ ID NO: 240	LCDR3 (IMGT)	QQSYSTPYT	
SEQ ID NO: 242	VL	DIQLTQPSSLSASVGDRVITICRASQSISYYLNWYQQKPGKAPKLLI-YAAS SLQSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQSYSTPYTFQGQGTK VEIK	
SEQ ID NO: 263	DNA VL	GACATCCAGCTCACCAAGTCCCCGAGCTCGCTGTCCGCCTCCGTGGGA GATCGGGTCACCATCACGTGCCGCCAGCAGTCGATTTCCCTAC CTGAACTGGTACCAACAGAACGCCGGAAAAGCCCCGAAGCTTCTCATC TACGCCGCCCTCGAGCTGCAGTCAGGAGTCGGCCTCACGGTTCTCCGGC TCCGGTTCCGTACTGATTTCACCCCTGACCATTTCCCTCCGCAACCGG AGGACTTCGCTACTACTACTGCCAGCAGTCGACTCCACCCCTACA CTTCGGACAAGGCACCAAGGTCGAATCAAG	
SEQ ID NO: 243	Linker	ASGGGGSGGGGGGGGG	
SEQ ID NO: 200	scFv (VH-linker-VL)	EVQLVESGGGLVQPGGSLRLSCAVSGFALS NHMSWVRAPGKGLEWV SGIVYSGSTYYAASVKGRTFISRDNSRNTLYLQMNSLRPEDTAI YYCSAHG GESDVWGQGTTTVSSASGGGGSGGGSGGGSDIQLTQPSSLSASVGD RVITICRASQSISYYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSG TDFTLTISLQPEDFATYYCQQSYSTPYTFQGQGTKVEIK	
SEQ ID NO: 201	DNA scFv	GAAGTGCAATTGGTGGAAATCAGGGGGAGGACTTGTGCAGCCTGGAGG ATCGCTGAGACTGTATGTGCCGTGTCGGCTTTGCCCTGTCACCCAC GGGATGTCTGGTCCGCCGCGCCTGGAAAGGGCTCGAATGGGT GTCGGGTATTGTGTACAGCGTAGCACCTACTATGCCGATCCGTGAA GGGGAGATTCCATCAGCGGGACAACCTCAGGAACACTCTGTACCT CCAATGAATTGCGTAGGCCAGAGGACACTGCCATCTACTACTGCTC CGCGCATGGCGGAGACTCGACGCTGGGACAGGGGACCACCGTGA CCGTGTCTAGCGCTCCGGCGAGCGGGCAGCGGGGTGGTGGTTCA GGGGCGCGGATCGGACATCCAGTCACCCAGTCCCCGAGCTCGCTG	

TABLE 22-continued

Amino acid sequences of exemplary components of dual CARs			
SEQ ID NO	Name/Description	Sequence	
		TCCGCCTCCGTGGGAGATCGGGTACCATCACGTGCCGCCAGCCAG TCGATTTCCTCTACCTGAACTGGTACCAACAGAACGCCGGAAAAGCC CGGAAGCTTCTCATCTACGCCCTCGAGCCTGCAGTCAGGAGTC TCACGGTTCTCCGGCTCGGTTCCGGTACTGATTTCACCCGTGACCATT CCTCCCTGCAACCGGAGGACTTCGTAACCTACTTGCCAGCAGTC ACTCCACCCCTACACTTCGGACAAGGCACCAAGGTCGAAATCAAG	
<u>duCD19.1</u>			
SEQ ID NO: 244	HCDR1	GVSLPDYGV	
SEQ ID NO: 245	HCDR2	VIWGSETTYQSSLKS	
SEQ ID NO: 246	HCDR3	HYYYGGSYAMDY	
SEQ ID NO: 295	(Kabat) HCDR1	DYGVS	
SEQ ID NO: 245	(Kabat) HCDR2	VIWGSETTYQSSLKS	
SEQ ID NO: 246	(Kabat) HCDR3	HYYYGGSYAMDY	
SEQ ID NO: 310	(Chothia) HCDR1	GVSLPDY	
SEQ ID NO: 311	(Chothia) HCDR2	WGSET	
SEQ ID NO: 246	(Chothia) HCDR3	HYYYGGSYAMDY	
SEQ ID NO: 312	(IMGT) HCDR1	GVSLPDYG	
SEQ ID NO: 313	(IMGT) HCDR2	IWGSETT	
SEQ ID NO: 314	(IMGT) HCDR3	AKHYYYGGSYAMDY	
SEQ ID NO: 250	VH	QVQLQESGPGLVKPSETLSLCTVSGVSLPDYGVSWIROPPGKLEWIGVI WGSETTYQSSLKSRVTISKDN SKNQVSLKLSSVTAADTAVYYCAKHYY YGGSYAMDYWGQGTLTVSS	
SEQ ID NO: 315	DNA VH	CAGGTCCAACCTCAAGAAAGCGGGACCGGGTCTTGTGAAGCCATCAGA AACTCTTCACTGACTTGTACTGTGAGCGGAGTGTCTCTCCCGATTAC GGGGTGTCTGGATCAGACAGCCACCGGGAAAGGGTCTGGAATGGAT TGGAGTGATTGGGGCTTGAGACTACTTACTACCAATCATCCCTCAA GTCACGGTCACCATCTCAAAGGACAACCTAAAGAATCAGGTGTCACT GAAACTGTCACTGTGACCGCAGCCGACACCGCCGTGTACTATTGCGC TAAGCATTAATTATGGCGGGAGCTACGCAATGGATTACTGGGACA GGGTACTCTGGTCACCGTGTCCAGC	
SEQ ID NO: 247	LCDR1	RASQDISKYLN	
SEQ ID NO: 248	LCDR2	HTSRLHS	
SEQ ID NO: 249	LCDR3	QQGNTLPYT	
SEQ ID NO: 247	(Kabat) LCDR1	RASQDISKYLN	
SEQ ID NO: 248	(Kabat) LCDR2	HTSRLHS	
SEQ ID NO: 249	(Kabat) LCDR3	QQGNTLPYT	

TABLE 22-continued

Amino acid sequences of exemplary components of dual CARs			
SEQ ID NO.	Name/Description	Sequence	
SEQ ID NO: 316	LCDR1 (Chothia)	SQDISKY	
SEQ ID NO: 317	LCDR2 (Chothia)	HTS	
SEQ ID NO: 318	LCDR3 (Chothia)	GNTLPY	
SEQ ID NO: 319	LCDR1 (IMGT)	QDISKY	
SEQ ID NO: 317	LCDR2 (IMGT)	HTS	
SEQ ID NO: 300	LCDR3 (IMGT)	QQGNTLPYT	
SEQ ID NO: 251	VL	EIVMTQSPATLSLSPGERATLSCRASQDISKYLNWYQQKPGQAPRLLIYHT SRLHSGIPARFSGSGSGTDYTLTISSLQPEDFAVYFCQQGNTLPYTFQGQT KLEIK	
SEQ ID NO: 320	DNA VL	GAAATTGTGATGACCCAGTCACCCGCCACTCTAGCCTTCAACCGGT GAGCGCCCAACCTGCTTGAGAGCCTCCAGACATCTCAAAATAC CTTAATTGGTATCAACAGAACGGCCAGGGCTCCATCTGGAAATCCCTGCCAGGTTCAGGGT TACCACACCAGCCGGCTCCATCTGGAAATCCCTGCCAGGTTCAGGGT AGCGGAATCTGGGACCCGACTACACCCCTCACTATCAGCTCACTGCAGCCA GAGGACTTCGCTGTCTATTCTGTAGCAAGGGAACACCCCTGCCCTAC ACCTTTGGACAGGGCACCAAGCTCGAGATAAAAGGTGGAGGTGGCAG CGGAGGAGGTGGTCCGGCGGTGGAGGAAGCCAGGTCCAACCTCAAG AAAGCGGACCGGGTCTTGTAAGGCAATCAGAAACTCTTCACTGACTT GTACTGTGAGCGGAGTGTCTCTCCCGATTACGGGTGCTTGGATCA GACAGCCACCGGGAAAGGGTCTGAATGGATTGGAGTGATTGGGGC TCTGAGACTTACTACCAATCATCCCTAAGTCACGCGTCACCATCT CAAAGGACAACCTAAAGAATCAGGTGACTGAAACTGTGACTCTGTGA CGCGAGCCACCGCGTGTACTATTGCGCTAAGCATTACTATTATG GCGGGAGCTACGCAATGGATTACTGGGACAGGGTACTCTGGTACCC GTGTCCAGC	
SEQ ID NO: 104	Linker	GGGGSGGGGGGGGS	
SEQ ID NO: 211	CAR2 scFv domain - aa (Linker is underlined)	EIVMTQSPATLSLSPGERATLSCRASQDISKYLNWYQQKPGQAPRLLIYHT SRLHSGIPARFSGSGSGTDYTLTISSLQPEDFAVYFCQQGNTLPYTFQGQT KLEIK <u>GGGGSGGGGGSGGGGSQVLQESGPGLVKPSETLSLTCTVSGVSLP</u> DYGVSWIRQPPKGLEWIGVIWGSETTYQSSLRVRTISKDNKNQVSL KLSSVTAADTAVYYCAKHYGGSYAMDYWQGQTLTVTSSTTPAPRP PTPAPTAISQPLSLRPEACRPAAGGAHVTRGLDFACDIYIWAPLAGTCGV LLSLVITLYCKGRKLLYIIFKQPMPRVQTTQEEEDGCSCRFPEEEE LRVKFRSRADAPAYQQQNQLYNELNLGRREEDYDVLDRGRDPEMGG KPRRKNPQEGLYNELQDKMAEAAYSEIGMKGERRRGKGHDGLYQGLST ATKD <b>TYDALHMQLP</b> R	
SEQ ID NO: 305	CAR2 scFv domain - nt	GAAATTGTGATGACCCAGTCACCCGCCACTCTAGCCTTCAACCGGT GAGCGCCCAACCTGCTTGAGAGCCTCCAGACATCTCAAAATAC CTTAATTGGTATCAACAGAACGGCCAGGGCTCCATCTGGAAATCCCTGCCAGGTTCAGGGT TACCACACCAGCCGGCTCCATCTGGAAATCCCTGCCAGGTTCAGGGT AGCGGAATCTGGGACCCGACTACACCCCTCACTATCAGCTCACTGCAGCCA GAGGACTTCGCTGTCTATTCTGTAGCAAGGGAACACCCCTGCCCTAC ACCTTTGGACAGGGCACCAAGCTCGAGATAAAAGGTGGAGGTGGCAG CGGAGGAGGTGGTCCGGCGGTGGAGGAAGCCAGGTCCAACCTCAAG AAAGCGGACCGGGTCTTGTAAGGCAATCAGAAACTCTTCACTGACTT GTACTGTGAGCGGAGTGTCTCTCCCGATTACGGGTGCTTGGATCA GACAGCCACCGGGAAAGGGTCTGAATGGATTGGAGTGATTGGGGC TCTGAGACTTACTACCAATCATCCCTAAGTCACGCGTCACCATCT CAAAGGACAACCTAAAGAATCAGGTGACTGAAACTGTGACTCTGTGA CGCGAGCCACCGCGTGTACTATTGCGCTAAGCATTACTATTATG GCGGGAGCTACGCAATGGATTACTGGGACAGGGTACTCTGGTACCC GTGTCCAGC	
SEQ ID NO: 225	Full CAR	EIVMTQSPATLSLSPGERATLSCRASQDISKYLNWYQQKPGQAPRLLIYHT SRLHSGIPARFSGSGSGTDYTLTISSLQPEDFAVYFCQQGNTLPYTFQGQT KLEIK <u>GGGGSGGGGGSGGGGSQVLQESGPGLVKPSETLSLTCTVSGVSLP</u> DYGVSWIRQPPKGLEWIGVIWGSETTYQSSLRVRTISKDNKNQVSL KLSSVTAADTAVYYCAKHYGGSYAMDYWQGQTLTVTSSTTPAPRP PTPAPTAISQPLSLRPEACRPAAGGAHVTRGLDFACDIYIWAPLAGTCGV LLSLVITLYCKGRKLLYIIFKQPMPRVQTTQEEEDGCSCRFPEEEE LRVKFRSRADAPAYQQQNQLYNELNLGRREEDYDVLDRGRDPEMGG KPRRKNPQEGLYNELQDKMAEAAYSEIGMKGERRRGKGHDGLYQGLST ATKD <b>TYDALHMQLP</b> R	

In some embodiments, disclosed herein is an isolated nucleic acid molecule comprising a first nucleic acid sequence encoding a first CAR polypeptide and a second nucleic acid sequence encoding a second CAR polypeptide, wherein the first CAR polypeptide comprises a first antigen-

binding domain which is an anti-BCMA binding domain (e.g., human anti-BCMA binding domain), a first transmembrane domain, and a first intracellular signaling domain, and wherein the second CAR polypeptide comprises a second antigen-binding domain which is an anti-CD 19 binding

domain, a second transmembrane domain, and a second intracellular signaling domain. In some embodiments, the first CAR polypeptide comprises a VH comprising a HC CDR1, HC CDR2, and HC CDR3 of an anti-BCMA sequence listed in Table 20 or 26 and a VL comprising a LC CDR1, LC CDR2, and LC CDR3 of an anti-BCMA sequence listed in Table 20 or 26, wherein the VH and VL are connected by a linker comprising the amino acid sequence of SEQ ID NO: 243. In some embodiment, the first CAR polypeptide comprises a VH and VL comprising the amino acid sequences of SEQ ID NOS: 239 and 242, respectively, wherein the VH and VL are connected by a linker comprising the amino acid sequence of SEQ ID NO: 243. In some embodiment, the first CAR polypeptide comprises an scFv comprising the amino acid sequence of SEQ ID NO: 200. In some embodiment, the first CAR polypeptide comprises the amino acid sequence of SEQ ID NO: 230 or 228. In some embodiments, the second CAR polypeptide comprises a HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and/or LC CDR3 of an anti-CD19 sequence listed in Table 19 or Table 22 (e.g., a HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprising the amino acid sequences of SEQ ID NOS: 295 and 245-249, respectively). In some embodiments, the second CAR polypeptide comprises a VH and/or VL of an anti-CD19 sequence listed in Table 19 or Table 22 (e.g., a VH and VL comprising the amino acid sequences of SEQ ID NOS: 250 and 251, respectively), or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the second CAR polypeptide comprises a scFv of an anti-CD19 sequence listed in Table 19 or Table 22 (e.g., a scFv comprising the amino acid sequence of SEQ ID NO: 211), or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the second CAR polypeptide comprises a CAR polypeptide of an anti-CD19 sequence listed in Table 19 or Table 22 (e.g., a CAR polypeptide comprising the amino acid sequence of SEQ ID NO: 225 or 229), or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the nucleic acid molecule comprises the nucleic acid sequence of SEQ ID NO: 221 or 223. In some embodiments, the nucleic acid molecule encodes the amino acid sequence of SEQ ID NO: 220 or 222, with or without the signal peptide of SEQ ID NO: 1.

#### Multi-Specific CARs

In an embodiment, a CAR of the invention is a multi-specific CAR. In one embodiment, the multi-specific CAR is a bispecific CAR. In one embodiment, the bispecific CAR comprises an antigen binding domain which is a bispecific antibody molecule. A bispecific antibody has specificity for no more than two antigens. A bispecific antibody molecule is characterized by a first immunoglobulin variable domain sequence which has binding specificity for a first epitope and a second immunoglobulin variable domain sequence that has binding specificity for a second epitope. In an embodiment, the first and second epitopes are on the same antigen, e.g., the same protein (or subunit of a multimeric protein). In an embodiment the first and second epitopes overlap. In an embodiment the first and second epitopes do not overlap. In an embodiment the first and second epitopes are on different antigens, e.g., different proteins (or different subunits of a multimeric protein). In an embodiment a bispecific antibody molecule comprises a heavy chain variable domain sequence and a light chain variable domain sequence which have binding specificity for a first epitope and a heavy chain variable domain sequence and a light chain variable domain

sequence which have binding specificity for a second epitope. In an embodiment a bispecific antibody molecule comprises a half antibody having binding specificity for a first epitope and a half antibody having binding specificity for a second epitope. In an embodiment a bispecific antibody molecule comprises a half antibody, or fragment thereof, having binding specificity for a first epitope and a half antibody, or fragment thereof, having binding specificity for a second epitope. In an embodiment a bispecific antibody molecule comprises a scFv, or fragment thereof, have binding specificity for a first epitope and a scFv, or fragment thereof, have binding specificity for a second epitope.

In some embodiments, a CAR of the invention comprises an antigen binding domain that is a multi-specific (e.g., a bispecific or a trispecific) antibody molecule. Protocols for generating bispecific or heterodimeric antibody molecules are known in the art; including but not limited to, for example, the “knob in a hole” approach described in, e.g., U.S. Pat. No. 5,731,168; the electrostatic steering Fc pairing as described in, e.g., WO 09/089004, WO 06/106905 and WO 2010/129304; Strand Exchange Engineered Domains (SEED) heterodimer formation as described in, e.g., WO 07/110205; Fab arm exchange as described in, e.g., WO 08/119353, WO 2011/131746, and WO 2013/060867; double antibody conjugate, e.g., by antibody cross-linking to generate a bi-specific structure using a heterobifunctional reagent having an amine-reactive group and a sulphydryl reactive group as described in, e.g., U.S. Pat. No. 4,433,059; bispecific antibody determinants generated by recombinant half antibodies (heavy-light chain pairs or Fabs) from different antibodies through cycle of reduction and oxidation of disulfide bonds between the two heavy chains, as described in, e.g., U.S. Pat. No. 4,444,878; trifunctional antibodies, e.g., three Fab' fragments cross-linked through sulphydryl reactive groups, as described in, e.g., U.S. Pat. No. 5,273,743; biosynthetic binding proteins, e.g., pair of scFvs cross-linked through C-terminal tails preferably through disulfide or amine-reactive chemical cross-linking, as described in, e.g., U.S. Pat. No. 5,534,254; bifunctional antibodies, e.g., Fab fragments with different binding specificities dimerized through leucine zippers (e.g., c-fos and c-jun) that have replaced the constant domain, as described in, e.g., U.S. Pat. No. 5,582,996; bispecific and oligospecific mono- and oligovalent receptors, e.g., VH-CH1 regions of two antibodies (two Fab fragments) linked through a polypeptide spacer between the CH1 region of one antibody and the VH region of the other antibody typically with associated light chains, as described in, e.g., U.S. Pat. No. 5,591,828; bispecific DNA-antibody conjugates, e.g., crosslinking of antibodies or Fab fragments through a double stranded piece of DNA, as described in, e.g., U.S. Pat. No. 5,635,602; bispecific fusion proteins, e.g., an expression construct containing two scFvs with a hydrophilic helical peptide linker between them and a full constant region, as described in, e.g., U.S. Pat. No. 5,637,481; multivalent and multispecific binding proteins, e.g., dimer of polypeptides having first domain with binding region of Ig heavy chain variable region, and second domain with binding region of Ig light chain variable region, generally termed diabodies (higher order structures are also encompassed creating for bispecific, trispecific, or tetraspecific molecules, as described in, e.g., U.S. Pat. No. 5,837,242; minibody constructs with linked VL and VH chains further connected with peptide spacers to an antibody hinge region and CH3 region, which can be dimerized to form bispecific/multivalent molecules, as described in, e.g., U.S. Pat. No. 5,837,821; VH and VL domains linked with a short peptide linker (e.g., 5 or 10 amino acids) or no linker at all

in either orientation, which can form dimers to form bispecific diabodies; trimers and tetramers, as described in, e.g., U.S. Pat. No. 5,844,094; String of VH domains (or VL domains in family members) connected by peptide linkages with crosslinkable groups at the C-terminus further associated with VL domains to form a series of FVs (or scFvs), as described in, e.g., U.S. Pat. No. 5,864,019; and single chain binding polypeptides with both a VH and a VL domain linked through a peptide linker are combined into multivalent structures through non-covalent or chemical crosslinking to form, e.g., homobivalent, heterobivalent, trivalent, and tetravalent structures using both scFV or diabody type format, as described in, e.g., U.S. Pat. No. 5,869,620.

Additional exemplary multispecific and bispecific molecules and methods of making the same are found, for example, in U.S. Pat. Nos. 5,910,573, 5,932,448, 5,959,083, 5,989,830, 6,005,079, 6,239,259, 6,294,353, 6,333,396, 6,476,198, 6,511,663, 6,670,453, 6,743,896, 6,809,185, 6,833,441, 7,129,330, 7,183,076, 7,521,056, 7,527,787, 7,534,866, 7,612,181, US2002004587A1, US2002076406A1, US2002103345A1, US2003207346A1, US2003211078A1, US2004219643A1, US2004220388A1, US2004242847A1, US2005003403A1, US2005004352A1, US2005069552A1, US2005079170A1, US2005100543A1, US2005136049A1, US2005136051A1, US2005163782A1, US2005266425A1, US2006083747A1, US2006120960A1, US2006204493A1, US2006263367A1, US2007004909A1, US2007087381A1, US2007128150A1, US2007141049A1, US2007154901A1, US2007274985A1, US2008050370A1, US2008069820A1, US2008152645A1, US2008171855A1, US2008241884A1, US2008254512A1, US2008260738A1, US2009130106A1, US2009148905A1, US2009155275A1, US2009162359A1, US2009162360A1, US2009175851A1, US2009175867A1, US2009232811A1, US2009234105A1, US2009263392A1, US2009274649A1, EP346087A2, WO0006605A2, WO02072635A2, WO04081051A1, WO06020258A2, WO2007044887A2, WO2007095338A2, WO2007137760A2, WO2008119353A1, WO2009021754A2, WO2009068630A1, WO9103493A1, WO9323537A1, WO9409131A1, WO9412625A2, WO9509917A1, WO9637621A2, WO9964460A1. The contents of the above-referenced applications are incorporated herein by reference in their entireties.

Within each antibody or antibody fragment (e.g., scFv) of a bispecific antibody molecule, the VH can be upstream or downstream of the VL. In some embodiments, the upstream antibody or antibody fragment (e.g., scFv) is arranged with its VH ( $VH_1$ ) upstream of its VL ( $VL_1$ ) and the downstream antibody or antibody fragment (e.g., scFv) is arranged with its VL ( $VL_2$ ) upstream of its VH ( $VH_2$ ), such that the overall bispecific antibody molecule has the arrangement  $VH_1-VL_1-VL_2-VH_2$ .

In other embodiments, the upstream antibody or antibody fragment (e.g., scFv) is arranged with its VL ( $VL_1$ ) upstream of its VH ( $VH_1$ ) and the downstream antibody or antibody fragment (e.g., scFv) is arranged with its VH ( $VH_2$ ) upstream of its VL ( $VL_2$ ), such that the overall bispecific antibody molecule has the arrangement  $VL_1-VH_1-VH_2-VL_2$ . Optionally, a linker is disposed between the two antibodies or antibody fragments (e.g., scFvs), e.g., between  $VL_1$  and  $VL_2$  if the construct is arranged as  $VH_1-VL_1-VL_2-VH_2$ , or between  $VH_1$  and  $VH_2$  if the construct is arranged as  $VL_1-VH_1-VH_2-VL_2$ . The linker may be a linker as described herein, e.g., a  $(Gly_4-Ser)_n$  linker, wherein n is 1, 2, 3, 4, 5, or 6, preferably 4 (SEQ ID NO: 26). In general, the linker between the two scFvs should be long enough to avoid mispairing between the domains of the two scFvs.

Optionally, a linker is disposed between the VL and VH of the first scFv. Optionally, a linker is disposed between the VL and VH of the second scFv. In constructs that have multiple linkers, any two or more of the linkers can be the same or different.

Accordingly, in some embodiments, a bispecific CAR comprises VLs, VHs, and optionally one or more linkers in an arrangement as described herein.

In one aspect, the bispecific antibody molecule is characterized by a first immunoglobulin variable domain sequence, e.g., a scFv, which has binding specificity for BCMA, e.g., comprises a scFv as described herein, or comprises the light chain CDRs and/or heavy chain CDRs from a BCMA scFv described herein, and a second immunoglobulin variable domain sequence that has binding specificity for a second epitope on a different antigen. In one aspect, the second immunoglobulin variable domain sequence has binding specificity for an antigen expressed on AML cells, e.g., an antigen other than BCMA. For example, the second immunoglobulin variable domain sequence has binding specificity for CD123. As another example, the second immunoglobulin variable domain sequence has binding specificity for CLL-1. As another example, the second immunoglobulin variable domain sequence has binding specificity for CD34. As another example, the second immunoglobulin variable domain sequence has binding specificity for FLT3. For example, the second immunoglobulin variable domain sequence has binding specificity for folate receptor beta. In some aspects, the second immunoglobulin variable domain sequence has binding specificity for an antigen expressed on B-cells, for example, CD10, CD19, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, or CD79a.

#### Diabody CAR

In some embodiments, a CAR of the invention is a bispecific CAR. In some embodiments, a CAR of the invention is a diabody CAR. In some embodiments, the diabody CAR comprises an antigen binding domain that binds to a first antigen and a second antigen. In some embodiments, the antigen binding domain comprises a VH1, a VL1, a VH2, and a VL2, wherein the VH1 and VL1 bind to the first antigen and the VH2 and VL2 bind to the second antigen. In some embodiments, the antigen binding domain has the arrangement VH1-optionally linker 1 ("L1")-VH2-optionally linker 2 ("L2")-VL2-optionally linker 3 ("L3")-VL1 from the N-terminus to the C-terminus. In some embodiments, the antigen binding domain has the arrangement VH1-optionally L1-VL2-optionally L2-VH2-optionally L3-VL1 from the N-terminus to the C-terminus. In some embodiments, the antigen binding domain has the arrangement VL1-optionally L1-VH2-optionally L2-VL2-optionally L3-VH1 from the N-terminus to the C-terminus. In some embodiments, the antigen binding domain has the arrangement VL1-optionally L1-VL2-optionally L2-VH2-optionally L3-VH1 from the N-terminus to the C-terminus. In some embodiments, the antigen binding domain has the arrangement VH2-optionally L1-VH1-optionally L2-VL1-optionally L3-VL2 from the N-terminus to the C-terminus. In some embodiments, the antigen binding domain has the arrangement VL2-optionally L1-VH1-optionally L2-VL1-optionally L3-VH2 from the N-terminus to the C-terminus. In some embodiments, the antigen binding domain has the arrangement VL2-optionally L1-VL1-optionally L2-VH1-optionally L3-VH2 from the N-terminus to the C-terminus.

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In some embodiments, the antigen binding domain has the arrangement VH1-linker 1 (“L1”)-VH2-linker 2 (“L2”)-VL2-linker 3 (“L3”)-VL1 from the N-terminus to the C-terminus. In some embodiments, the antigen binding domain has the arrangement VH1-L1-VL2-L2-VH2-L3-VL1 from the N-terminus to the C-terminus. In some embodiments, the antigen binding domain has the arrangement VL1-L1-VH2-L2-VL2-L3-VH1 from the N-terminus to the C-terminus. In some embodiments, the antigen binding domain has the arrangement VL1-L1-VL2-L2-VH2-L3-VH1 from the N-terminus to the C-terminus. In some embodiments, the antigen binding domain has the arrangement VH2-L1-VH1-L2-VL1-L3-VL2 from the N-terminus to the C-terminus. In some embodiments, the antigen binding domain has the arrangement VL2-L1-VH1-L2-VL1-L3-VH2 from the N-terminus to the C-terminus. In some embodiments, the antigen binding domain has the arrangement VL2-L1-VL1-L2-VH1-L3-VH2 from the N-terminus to the C-terminus. In some embodiments, the variable regions are fused by a linker comprising the amino acid sequence of GGGGSGGGGS (SEQ ID NO: 5). In some embodiments, the variable regions are fused by a linker comprising the amino acid sequence of GGGGSGGGSGGGGSGGGGS (SEQ ID NO: 63). In some embodiments, L1 comprises the amino acid sequence of SEQ ID NO: 5. In some embodiments, L2 comprises the amino acid sequence of SEQ ID NO: 63. In some embodiments, L3 comprises the amino acid sequence of SEQ ID NO: 5. In some embodiments, the VH1, VL1, VH2, or VL2 comprises a CDR, a VH, or a VL sequence disclosed herein, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, a diabody disclosed herein comprises an engineered disulfide bridge, e.g., to stabilize the diabody and/or to facilitate correct pairing of the VH and VL. In some embodiments, the engineered disulfide bridge is between the variable region that is most proximal to the hinge region (e.g., the VH or VL region that is most proximal to the hinge region) and its corresponding pairing partner (e.g., the corresponding VL or the corresponding VH).

In some embodiments, the first antigen and the second antigen are different. In some embodiments, the first or second antigen is chosen from an antigen expressed on B cells, an antigen expressed on acute myeloid leukemia cells, or an antigen on solid tumor cells. In some embodiments, the first or second antigen is chosen from CD10, CD19, CD20, CD22, CD34, CD123, BCMA, FLT-3, ROR1, CD79b, CD179b, CD79a, CD34, CLL-1, folate receptor beta, FLT3, EGFRvIII, mesothelin, GD2, Tn antigen, sTn antigen, Tn-O-Glycopeptides, sTn-O-Glycopeptides, PSMA, CD97, TAG72, CD44v6, CEA, EPCAM, KIT, IL-13Ra2, leguman, GD3, CD171, IL-11Ra, PSCA, MAD-CT-1, MAD-CT-2, VEGFR2, LewisY, CD24, PDGFR-beta, SSEA-4, folate receptor alpha, ERBBs (e.g., ERBB2), Her2/neu, MUC1, EGFR, NCAM, Ephrin B2, CAIX, LMP2, sLe, HMWMAA, o-acetyl-GD2, folate receptor beta, TEM1/CD248, TEM7R, FAP, Legumain, HPV E6 or E7, ML-IAP, CLDN6, TSHR, GPRC5D, ALK, Polysialic acid, Fos-related antigen, neutrophil elastase, TRP-2, CYP1B1, sperm protein 17, beta human chorionic gonadotropin, AFP, thyroglobulin, PLAC1, globoH, RAGE1, MN-CA IX, human telomerase reverse transcriptase, intestinal carboxyl esterase, mut hsp 70-2, NA-17, NY-BR-1, UPK2, HAVCR1, ADRB3, PANX3, NY-ESO-1, GPR20, Ly6k, OR51E2, TARP, GFR $\alpha$ 4, or a peptide of any of these antigens presented on MHC.

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In some embodiments, the first antigen is BCMA and the second antigen is CD19. In some embodiments, the CAR comprises an antigen binding domain that binds to BCMA and CD19. In some embodiments, the antigen binding domain comprises a VH<sub>1</sub> and a VL<sub>1</sub> that bind to BCMA (“BCMA VH” and “BCMA VL”) and a VH<sub>2</sub> and a VL<sub>2</sub> that bind to CD19 (“CD19 VH” and “CD19 VL”). In some embodiments, the antigen binding domain has the arrangement BCMA VH-optionally linker 1 (“L1”)-CD19 VH-optionally linker 2 (“L2”)-CD19 VL-optionally linker 3 (“L3”)-BCMA VL from the N-terminus to the C-terminus. In some embodiments, the antigen binding domain has the arrangement BCMA VH-optionally L1-CD19 VL-optionally L2-CD19 VH-optionally L3-BCMA VL from the N-terminus to the C-terminus. In some embodiments, the antigen binding domain has the arrangement BCMA VL-optionally L1-CD19 VL-optionally L2-CD19 VH-optionally L3-BCMA VH from the N-terminus to the C-terminus. In some embodiments, the antigen binding domain has the arrangement BCMA VL-optionally L1-CD19 VL-optionally L2-CD19 VH-optionally L3-BCMA VL from the N-terminus to the C-terminus. In some embodiments, the antigen binding domain has the arrangement BCMA VH-optionally L1-BCMA VL-optionally L2-BCMA VH-optionally L3-CD19 VL from the N-terminus to the C-terminus. In some embodiments, the antigen binding domain has the arrangement BCMA VH-optionally L1-BCMA VL-optionally L2-BCMA VL-optionally L3-CD19 VH from the N-terminus to the C-terminus. In some embodiments, the antigen binding domain has the arrangement BCMA VH-linker 1 (“L1”)-CD19 VH-linker 2 (“L2”)-CD19 VL-linker 3 (“L3”)-BCMA VL from the N-terminus to the C-terminus. In some embodiments, the antigen binding domain has the arrangement BCMA VH-L1-CD19 VL-L2-CD19 VH-L3-BCMA VL from the N-terminus to the C-terminus. In some embodiments, the antigen binding domain has the arrangement BCMA VL-L1-CD19 VH-L2-CD19 VL-L3-BCMA VH from the N-terminus to the C-terminus. In some embodiments, the antigen binding domain has the arrangement BCMA VL-L1-CD19 VL-L2-CD19 VH-L3-BCMA VL from the N-terminus to the C-terminus. In some embodiments, the antigen binding domain has the arrangement BCMA VL-L1-CD19 VL-L2-CD19 VH-L3-CD19 VL from the N-terminus to the C-terminus. In some embodiments, the antigen binding domain has the arrangement BCMA VL-L1-BCMA VH-L2-BCMA VL-L3-CD19 VL from the N-terminus to the C-terminus. In some embodiments, the antigen binding domain has the arrangement BCMA VL-L1-BCMA VH-L2-BCMA VL-L3-CD19 VH from the N-terminus to the C-terminus. In some embodiments, the antigen binding domain has the arrangement BCMA VL-L1-BCMA VL-L2-BCMA VH-L3-CD19 VL from the N-terminus to the C-terminus. In some embodiments, the antigen binding domain has the arrangement BCMA VL-L1-BCMA VL-L2-BCMA VL-L3-CD19 VH from the N-terminus to the C-terminus. In some embodiments, the variable regions are fused by a linker comprising the amino acid sequence of SEQ ID NO: 5 or 63, or an amino acid sequence having at least 80, 85, 90, 95, or 99% identity thereto. In some embodiments, L1 comprises the amino acid sequence of SEQ ID NO: 5. In some embodiments, L2

comprises the amino acid sequence of SEQ ID NO: 63. In some embodiments, L3 comprises the amino acid sequence of SEQ ID NO: 5.

In some embodiments, the BCMA VH comprises CDR or VH sequences disclosed herein, e.g., CDR or VH sequences disclosed in Tables 3-15, 19, 20, 22, 26, and 31, or an amino acid sequence having at least 80, 85, 90, 95, or 99% identity thereto. In some embodiments, the BCMA VL comprises CDR or VL sequences disclosed herein, e.g., CDR or VL sequences disclosed in Tables 3-15, 19, 20, 22, 26, and 31, or an amino acid sequence having at least 80, 85, 90, 95, or 99% identity thereto. In some embodiments, the CD19 VH comprises CDR or VH sequences disclosed herein, e.g., CDR or VH sequences disclosed in Tables 2, 19, 22, and 31, or an amino acid sequence having at least 80, 85, 90, 95, or 99% identity thereto. In some embodiments, the CD19 VL comprises CDR or VL sequences disclosed herein, e.g., CDR or VL sequences disclosed in Tables 2, 19, 22, and 31, or an amino acid sequence having at least 80, 85, 90, 95, or 99% identity thereto.

In some embodiments, the CAR, e.g., a diabody CAR, further comprises a hinge region, a transmembrane domain, and/or an intracellular signaling domain. In some embodiments, the hinge region comprises a CD8 hinge region. In some embodiments, the hinge region comprises a hinge region sequence disclosed herein, e.g., the amino acid sequence of SEQ ID NO: 2, or an amino acid sequence having at least 80, 85, 90, 95, or 99% identity thereto. In

some embodiments, the transmembrane domain comprises a CD8 transmembrane domain. In some embodiments, the transmembrane domain comprises a transmembrane domain sequence disclosed herein, e.g., the amino acid sequence of SEQ ID NO: 6, or an amino acid sequence having at least 80, 85, 90, 95, or 99% identity thereto. In some embodiments, the intracellular signaling domain comprises a 4-1BB intracellular domain. In some embodiments, the intracellular signaling domain comprises a costimulatory signaling domain sequence disclosed herein, e.g., the amino acid sequence of SEQ ID NO: 7, or an amino acid sequence having at least 80, 85, 90, 95, or 99% identity thereto. In some embodiments, the intracellular signaling domain comprises a CD3 intracellular domain. In some embodiments, the intracellular signaling domain comprises a primary signaling domain sequence disclosed herein, e.g., the amino acid sequence of SEQ ID NO: 9 or 10, or an amino acid sequence having at least 80, 85, 90, 95, or 99% identity thereto.

Exemplary diabody sequences are disclosed in Table 31. In some embodiments, the CAR comprises an antigen binding domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 321-330, or an amino acid sequence having at least 80, 85, 90, 95, or 99% identity thereto. In some embodiments, the CAR comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 339-348, or an amino acid sequence having at least 80, 85, 90, 95, or 99% identity thereto.

TABLE 31

## Exemplary components of diabody CARs.

SEQ ID NO	Description	Amino acid sequence*
SEQ ID NO: 321	JL1 antigen binding domain	<u>QVQLQESGPGLVKPSETLSLTCTVSGVSLPDYGVSWIRQPPGKCLEWIGVIWGS</u> <u>ETTYYQSSLKSRVTISKDNNSKNQVSLKLSSVTAADTAVYYCAKHYYGGSYAMDY</u> <u>WGCGTLYQSSGGGSQSLTQPASVSGSPGQSITISCTGTSSDVGGYNVVS</u> <u>WYQOHPGKAPKLMIDYDSNRPSGVNRESGSKSGNTASLTISGLQAEDEAD</u> <u>YCSSSYTSSSTLYVFSGSGTKVTVLGGGGSGGGGSQGGGSGGGSQVQLOE</u> <u>SGGGVVPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWAVISYDGS</u> <u>NKYYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAVYYCGGSGYALHD</u> <u>DYYGLDVGWQGTLTVTSSGGGSEIVMTOSPATLSPGERATLSCRASQDIS</u> <u>KYLNWYQQKPGQAPRLLIYHTSRLHSGIPARFSGSGSGTDYTLTISSLQPEDFAV</u> <u>YFCQOGNTLPYTFGCGTKLEIK</u>
SEQ ID NO: 339	JL1 full length diabody CAR	<u>QVQLQESGPGLVKPSETLSLTCTVSGVSLPDYGVSWIRQPPGKCLEWIGVI</u> <u>WGSETTYYQSSLKSRVTISKDNNSKNQVSLKLSSVTAADTAVYYCAKHYY</u> <u>GGSYAMDYWQGQTLTVTSSGGGSGQSLTQPASVSGSPGQSITISCTGTSS</u> <u>DVGGYNYVSWYQOHPGKAPKLMIDYDSNRPSGVNRFSGSKSGNTASLTI</u> <u>SGLQAEDADYYCSSSYTSSSTLYVFSGSGTKVTVLGGGGSGGGGSQGGGSG</u> <u>GGGSQVQLQESGGGVVQPGRSRLSCAASGFTFSSYGMHWVRQAPGKGL</u> <u>EWVAVISYDGSNKYYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAVYY</u> <u>CGGSGYALHDYYGLDWGQGTLTVTSSGGGSEIVMTOSPATLSPGE</u> <u>RATLSCRASQDISKYLNWYQQKPGQAPRLLIYHTSRLHSGIPARFSGSGSGT</u> <u>DYTLTISSLQPEDFAVYFCQOGNTLPYTFGCGTKLEIKTTTPAPRPPTAPT</u> <u>ASQPLSLRPEACRPAAGGAHVTRGLDFACDIYIWAPLAGTCVGLLSSLVITL</u> <u>YCKRGRKLLYI FKQPFMRPVQTTQBEDGCSRFPFEEEGCIELRVKESRS</u> <u>ADAPAYKQGQNQLYNELNLRGEEYDVLDKRRGRDPMEMGGKPRRKNPQE</u> <u>GLYNELQDKDMAEAYSEIGMKGERRRGKGDGLYQGLSTATKDTYDALH</u> <u>MQALPPR</u>
SEQ ID NO: 322	JL2 antigen binding domain	<u>EIVMTQSPATLSPGERATLSCRASQDISKYLNWYQQKPGQAPRLLIYHTSRLHS</u> <u>GIPARFSGSGSGTDYTLTISSLQPEDFAVYFCQOGNTLPYTFGCGTKLEIKGGGG</u> <u>SOVQLQESGGGVVQPGRSRLSCAASGFTFSSYGMHWVRQAPGKGLEWV</u> <u>AVISYDGSNKYYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAVYYCGG</u> <u>SGYALHDYYGLDWGQGTLTVTSSGGGSGGGSGGGSGGGSGGGSGSA</u> <u>LTOQASVSGSPGQSITISCTGTSSDVCGYNYVSWYQOHPGKAPKLMIDYDS</u> <u>NRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSSYTSSSTLYFGSGT</u> <u>KVTVLGGGGSQVQLQESGPGLVKPSETLSLTCTVSGVSLPDYGVSWIRQPPGK</u> <u>CLEWIGVIWGSSETTYQSSLKSRVTISKDNNSKNQVSLKLSSVTAADTAVYYCAHY</u> <u>YYGGSYAMDYWGQGTLTVVSS</u>
SEQ ID NO:	JL2 full	EIVMTQSPATLSPGERATLSCRASQDISKYLNWYQQKPGQAPRLLIYHTS

TABLE 31-continued

Exemplary components of diabody CARs.			
SEQ ID NO	Description	Amino acid sequence*	
NO: 340	length diabody CAR	<p>RLHSGIPARFSGSGSGTDTLTLTSSLQPEDFAVYFCQQGNTLPYTFCGCTKL  EIKGGGGSQVQLQESGGGVVQPGRSRRLSCAASGFTFSSYGMHWVRQAPG  KGELEWAVISDGSKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTA  VYCCGGSGYALHDYYGLDWGQGTLTVTSSGGGGSGGGGGGGGGGG  GGSQSALTQPAVSVGSPGQSITISCTGTSSDVGGNYVSWYQOHPGKAPKL  MIYDVSNRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSTLY  VFGSGTKVTVLGCGGSQVQLQESGPGLVKPSETLSLTCTVSGVSLPDYGV  WIRQPPGKCLEWIGVWQGTLTVTSSSSTTTAPRPPPTAPIAS  QPLSLRPEACRPAAGGAHVTRGLDFACDIYIWAPLAGTCGVLLSLVITLY  CKRGRKKLLYIFKQPFMRPVQTQEEDGCSRFPEEEAGGCELRVKFSRSA  DAPAYKQGQNQLYNELNLGRREYDVLDRGRDPEMGGKPRRNQEG  LYNELQDKDMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALH  MQALPPR</p>	
SEQ ID NO: 323	JL3 antigen binding domain	<p>QVQLQESGPGLVKPSETLSLCTVSGVSLPDYGVWIRQPPGKCLEWIGVW  ETTYYQSSLKSRVTISKDN SKNQVSLKLSVTAAADTAVYYCAKHYYGGSYAMDY  WGQGTLTVTSSGGGGSQVQLQESGGGVVQPGRSRRLSCAASGFTFSSYGMH  WVRQAPGKGLEWVAVISYDGSKYYADSVKGRFTISRDN SKNTLYLQMN  SLRAEDTA  VYCCGGSGYALHDYYGLDWGQGTLTVTSSGGGGGGGGGG  GGGGGGGGGGSQSALTQPAVSVGSPGQSITISCTGTSSDVGGNYVSWYQO  HPGKAPKLMIDVSNRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCS  SYTSSSTLYVFGSGTKVTVLGCGGSITIVMTOSPATLSLSPGERATLSCRASODI  SKYLNWYQOKPGQAPRLLIYHTSRLHS  GIPARFSGSGSGTDTLTLTSSLQPEDFAVYFCQQGNTLPYTFCGCTKLEIKGGGG  YFCQOGNTLPYTFCGCTKLEIK</p>	
SEQ ID NO: 341	JL3 full length diabody CAR	<p>QVQLQESGPGLVKPSETLSLCTVSGVSLPDYGVWIRQPPGKCLEWIGV  WGSETTYYQSSLKSRVTISKDN SKNQVSLKLSVTAAADTAVYYCAKHYY  GGSYAMDYWGQGTLTVTSSGGGGSQVQLQESGGGVVQPGRSRRLSCAAS  GFTFSSYGMHWVRQAPGKGLEWVAVISYDGSKYYADSVKGRFTISRDN  SKNTLYLQMN SLRAEDTA  VYCCGGSGYALHDYYGLDWGQGTLTVTSSGGGGGGGGGGGGGGGGGGGG  GG  YNYVSWYQOHPGKAPKLMIDVSNRPSGVSNRFSGSKSGNTASLTISGLQ  AEDEADYYCSSYTSSTLYVFGSGTKVTVLGCGGSIEVMTQS PATLSPGE  RATLSCRASODI SKYLNWYQOKPGQAPRLLIYHTSRLHS  GIPARFSGSGSGTDTLTLTSSLQPEDFAVYFCQQGNTLPYTFCGCTKLEIK  ASQPLSLRPEACRPAAGGAHVTRGLDFACDIYIWAPLAGTCGVLLSLVITL  YCKRGRKKLLYIFKQPFMRPVQTQEEDGCSRFPEEEAGGCELRVKFSRSA  DAPAYKQGQNQLYNELNLGRREYDVLDRGRDPEMGGKPRRNQEG  LYNELQDKDMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALH  MQALPPR</p>	
SEQ ID NO: 324	JL4 antigen binding domain	<p>EIVMTOSPATLSSLSPGERATLSCRASODISKYLNWYQOKPGQAPRLLIYHTSRLHS  GIPARFSGSGSGTDTLTLTSSLQPEDFAVYFCQQGNTLPYTFCGCTKLEIKGGGG  SQSALTQPAVSVGSPGQSITISCTGTSSDVGGNYVSWYQOHPGKAPKLM  YDVSNRPSGVSNRESGSKSGNTASLTISGLQAEDEADYYCSSYTSSTLYV  GSGTKVTVLGCGGSGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG  SCAASGFTTESSYGMHWVRQAPGKGLEWVAVISYDGSKYYADSVKGRFTI  SRDN SKNTLYLQMN SLRAEDTA  VYCCGGSGYALHDYYGLDWGQGTLTVTSSGGGGSQVQLQESGPGLVKPSETLSLCTVSGVSLPDYGVWIRQPPGK  CLEWIGVWQGTLTVTSSGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG  YYGGSYAMDYWGQGTLTVTSS</p>	
SEQ ID NO: 342	JL4 full length diabody CAR	<p>EIVMTOSPATLSSLSPGERATLSCRASODISKYLNWYQOKPGQAPRLLIYHTS  RLHSGIPARFSGSGSGTDTLTLTSSLQPEDFAVYFCQQGNTLPYTFCGCTKL  EIKGGGGSQSALTQPAVSVGSPGQSITISCTGTSSDVGGNYVSWYQOHPG  KAPKLMIDVSNRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSY  SSTLYVFGSGTKVTVLGCGGSGGGGGGGGGGGGGGGGGGGGGGGGGGGG  PGRSLRSLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSKYYAD  VKGRFTISRDN SKNTLYLQMN SLRAEDTA  VYCCGGSGYALHDYYGLDWGQGTLTVTSSGGGGSQVQLQESGPGLVKPSETLSLCTVSGVSLPDYGV  WIRQPPGKCLEWIGVWQGTLTVTSSSSTTTAPRPPPTAPIAS  QPLSLRPEACRPAAGGAHVTRGLDFACDIYIWAPLAGTCGVLLSLVITLY  CKRGRKKLLYIFKQPFMRPVQTQEEDGCSRFPEEEAGGCELRVKFSRSA  DAPAYKQGQNQLYNELNLGRREYDVLDRGRDPEMGGKPRRNQEG  LYNELQDKDMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALH  MQALPPR</p>	
SEQ ID NO: 325	JL5 antigen binding domain	<p>QVQLQESGGGVVQPGRSRRLSCAASGFTFSSYGMHWVRQAPGKCLEWVA  VISYDGSKYYADSVKGRFTISRDN SKNTLYLQMN SLRAEDTA  VYCCGGSGYALHDYYGLDWGQGTLTVTSSGGGGSEIIVMTOSPATLSSLSPGERATL  CRASODISKYLNWYQOKPGQAPRLLIYHTSRLHS  GIPARFSGSGSGTDTLTLTSSLQPEDFAVYFCQQGNTLPYTFCGCTKLEIKGGGGGGGGGGGGGGGGGGGGGGGGGGGG  QPLSLRPEACRPAAGGAHVTRGLDFACDIYIWAPLAGTCGVLLSLVITLY  CKRGRKKLLYIFKQPFMRPVQTQEEDGCSRFPEEEAGGCELRVKFSRSA  DAPAYKQGQNQLYNELNLGRREYDVLDRGRDPEMGGKPRRNQEG  LYNELQDKDMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALH  MQALPPR</p>	

TABLE 31-continued

Exemplary components of diabody CARs.		
SEQ ID NO	Description	Amino acid sequence*
		<u>YYQSSLKSRVTISKDNSKNQVSLKLSSVTAADTAVYYCAKHYYYGGSYAMDYWQG</u> <u>GTLVTSSGGGGSQSALTQPVASVSGSPGQSITISCTGTSSDVGYYNYVSWYQ</u> <u>QHPGKAPKLMIYDVSNRPSGVSNRESGSKSGNTASLTISLQAEDEADYYC</u> <u>SYTSSSTLYVFCGCKTVL</u>
SEQ ID NO: 343	JL5 full length diabody CAR	QVQLQESGGVVQPGRSRLSCAASGTFSSYGMHWVRQAPGKCLEWVA VISYDGSKNKYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCGGS GYALHDDYYGLDVWQGQTLTVTSSGGGGSEIVMTQSPATLSSPGERATL SCRASQDISKYLNWYQQKPGQAPRLLIYHTSRLHSGIPARFSGSGSGTDYTL TISSLQPEDFAVYFCQQGNTLPYTFQGQTKLEIKGGGGSGGGGGSGGG GGSQVQLQESPGPLVKPSETLSLTCTVSGVSLPDYGVSWIRQPPGKGLEWI GVIWGSEETTYQSSLKSRVTISKDNSKNQVSLKLSSVTAADTAVYYCAK YYGGSYAMDYWQGQTLTVTSSGGGGSQSALTQPVASVSGSPGQSITISCT GTSSDVGYYNYVSWYQQHPGKAPKLMIYDVSNRPSGVSNRFSGSKSGNTA SLTISLQAEDEADYYCSSTSYTSSSTLYVFCGCKTVLTTTPAPRPPPTPAPTI ASQPLSLRPEACRPAAGGAHVTRGLDFACDIYIWAPLAGTCGVLLSLVITL YCKRGRKKLLYIFKQPFMRPVQTQEDGCSRFPEEEAGGCERLVKFRS ADAPAYKQGQNQLYNELNLRREEYDVLKRRGRDPEMGGKPRRKNPQE GLYNELQDKDMAEAYSEIGMKGERRRGKGDGLYQGLSTATKDTYDALH MQALPPR
SEQ ID NO: 326	JL6 antigen binding domain	<u>QSALTQPVASVSGSPGQSITISCTGTSSDVGYYNYVSWYQQHPGKAPKLMIY</u> <u>DVSNRPSGVSNRESGSKSGNTASLTISLQAEDEADYYCSSTSYTSSSTLYVFG</u> <u>CGTKVTVLGGGGSQVQLQESPGPLVKPSETLSLTCTVSGVSLPDYGVSWIRQ</u> <u>PCKGLEWIGVWGEETTYQSSLKSRVTISKDNSKNQVSLKLSSVTAADTAVYYCA</u> <u>KHYYYGGSYAMDYWQGQTLTVTSSGGGGSGGGGGSGGGGGSEIVMTOS</u> <u>PATLSSPGERATLSCRASQDISKYLNWYQQKPGQAPRLLIYHTSRLHSGIPARES</u> <u>GSGSGTDYTLTISLQPEDFAVYFCQQGNTLPYTFQGQTKLEIKGGGGSQVQ</u> <u>QESGGVVQPGRSRLSCAASGTFSSYGMHWVRQAPGKCLEWVAISYD</u> <u>GSNKYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCGGSGYAL</u> <u>HDDYYGLDVWQGQTLTVTSS</u>
SEQ ID NO: 344	JL6 full length diabody CAR	QSALTQPVASVSGSPGQSITISCTGTSSDVGYYNYVSWYQQHPGKAPKLMIY DVSNRPSGVSNRESGSKSGNTASLTISLQAEDEADYYCSSTSYTSSSTLYVFG CGTKVTVLGGGGSQVQLQESPGPLVKPSETLSLTCTVSGVSLPDYGVSWIR QPPGKGLEWIGVWGEETTYQSSLKSRVTISKDNSKNQVSLKLSSVTAAD TAVYYCAKHYYYGGSYAMDYWQGQTLTVTSSGGGGSGGGGGSGGGGG GGSSEIVMTQSPATLSSPGERATLSCRASQDISKYLNWYQQKPGQAPRLLIY HTSRLHSGIPARFSGSGSGTDYTLTISLQPEDFAVYFCQQGNTLPYTFQG TKLEIKGGGGSQVQLQESGGGVVQPGRSRLSCAASGFTSSYGMHWVRQ APGKCLEWVAISYDGSKNKYADSVKGRFTISRDNSKNTLYLQMNSLRAE DTAVYYCGGSGYALHDYYGLDVWQGQTLTVTSSSTTPAPRPPPTPAPTI SQPLSLRPEACRPAAGGAHVTRGLDFACDIYIWAPLAGTCGVLLSLVITL YCKRGRKKLLYIFKQPFMRPVQTQEDGCSRFPEEEAGGCERLVKFRS ADAPAYKQGQNQLYNELNLRREEYDVLKRRGRDPEMGGKPRRKNPQE LYNELQDKDMAEAYSEIGMKGERRRGKGDGLYQGLSTATKDTYDALH MQALPPR
SEQ ID NO: 327	JL7 antigen binding domain	QVQLQESGGVVQPGRSRLSCAASGTFSSYGMHWVRQAPGKCLEWVA VISYDGSKNKYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCGGS GYALHDDYYGLDVWQGQTLTVTSSGGGGSQVQLQESPGPLVKPSETLSLT TVSGVSLPDYGVSWIRQPPGKGLEWIGVWGEETTYQSSLKSRVTISKDNSKN VSLKLSSVTAADTAVYYCAKHYYYGGSYAMDYWQGQTLTVTSSGGGGSGGG GCGGGSGGGSEIVMTQSPATLSSPGERATLSCRASQDISKYLNWYQQKPGQ PRLLIYHTSRLHSGIPARFSGSGSGTDYTLTISLQPEDFAVYFCQQGNTLPYTF QGTFKLEIKGGGGSQSALTQPVASVSGSPGQSITISCTGTSSDVGYYNYVSWYQ QHPGKAPKLMIYDVSNRPSGVSNRESGSKSGNTASLTISLQAEDEADYYC SYTSSSTLYVFCGCKTVL
SEQ ID NO: 345	JL7 full length diabody CAR	QVQLQESGGVVQPGRSRLSCAASGTFSSYGMHWVRQAPGKCLEWVA VISYDGSKNKYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCGGS GYALHDDYYGLDVWQGQTLTVTSSGGGGSQVQLQESPGPLVKPSETLSLT CTVSGVSLPDYGVSWIRQPPGKGLEWIGVWGEETTYQSSLKSRVTISKD NSKNQVSLKLSSVTAADTAVYYCAKHYYYGGSYAMDYWQGQTLTVSS GGGGSGGGGGSGGGGGSGGGSEIVMTQSPATLSSPGERATLSCRASQDIS YLNWYQQKPGQAPRLLIYHTSRLHSGIPARFSGSGSGTDYTLTISLQPEDF AVYFCQQGNTLPYTFQGQTKLEIKGGGGSQSALTQPVASVSGSPGQSITISCT GTSSDVGYYNYVSWYQQHPGKAPKLMIYDVSNRPSGVSNRFSGSKSGNTA SLTISLQAEDEADYYCSSTSYTSSSTLYVFCGCKTVLTTTPAPRPPPTPAPTI ASQPLSLRPEACRPAAGGAHVTRGLDFACDIYIWAPLAGTCGVLLSLVITL YCKRGRKKLLYIFKQPFMRPVQTQEDGCSRFPEEEAGGCERLVKFRS ADAPAYKQGQNQLYNELNLRREEYDVLKRRGRDPEMGGKPRRKNPQE GLYNELQDKDMAEAYSEIGMKGERRRGKGDGLYQGLSTATKDTYDALH MQALPPR

TABLE 31-continued

Exemplary components of diabody CARs.		
SEQ ID NO	Description	Amino acid sequence*
SEQ ID NO: 328	JL8 antigen binding domain	QSALTQPVASVGSPGQSTITISCTGTSSDVGGNYVSWYQOHPGKAPKLMY DVSNRPSGVSNRSGSKSGNTASLTISGLQAEDADYYCSSYTSSSTLVFG <u>CGTKVTVLGGGSEIVMTQSPATLSLSPGERATLSCRASODISKYLNWYQQP</u> <u>GQAPRLLIYHTSRLHSGTIPARFSGSGSGTDYTLTISSLQPEDFAVYFCQOGN</u> <u>TLPYTFGCGTKLEIKGGGGSGGGGGGGGSQVQLQESGPGLVKPSETLSLT</u> <u>CTVSGVSLPDYGVSWIRQPPGKGLEWIGVIWGETTYQSSLKSRVTISKDNSKN</u> <u>QVSLKLSSVTAADTAVVYCAKHYYGGSYAMDYWGQGTLVTVSSGGGGSQVQL</u> <u>QESGGGGVQGRSLRLSCAASGFTFSSYGMHWVRQAPGKCLEWVAVISYD</u> <u>GSNKYVADSVKGRFTISRDNSKNTLYLQMNLSRAEDTAVVYCGGSGYAL</u> <u>HDDYYGLDVWGQGTLVTVSS</u>
SEQ ID NO: 346	JL8 full length diabody CAR	QSALTQPVASVGSPGQSTITISCTGTSSDVGGNYVSWYQOHPGKAPKLMY DVSNRPSGVSNRSGSKSGNTASLTISGLQAEDADYYCSSYTSSSTLVFG CGTKVTVLGGGSEIVMTQSPATLSLSPGERATLSCRASODISKYLNWYQQ KPGQAPRLLIYHTSRLHSGTIPARFSGSGSGTDYTLTISSLQPEDFAVYFCQQG NTLPYTFGCGTKLEIKGGGGSGGGGGGGGSQVQLQESGPGLVKP SETSLTCTVSGVSLPDYGVSWIRQPPGKGLEWIGVIWGETTYQSSLKSR VTISKDNNSKNQVSLKLSSVTAADTAVVYCAKHYYGGSYAMDYWGQGTL VTVSSGGGGSQVQLQESGGGVQPGRSRLRLSCAASGFTFSYGMHWVRQ APGKCLEWVAVISYDGSNKYADSVKGRFTISRDNSKNTLYLQMNLSRAE DTAVVYGGSGYALHDYYGLDVWGQGTLVTVSSSTTPAPRPTPA SQPLSLRPEACRPAAGGAHVTRGLDFACDIYIWAPLAGTCGVLLLSLVITL CKRGRKKLLYIFKQPFMRPVQTQEEDGCSRFPPEEEEGGCERVKFSRSA DAPAYKQGQNQLYNELNLGRREEVYDVLDKRRGRDPEMGGKPRRNQEG LYNELQDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALH MQALPPR
SEQ ID NO: 329	JL9 antigen binding domain	QVQLQESGPGLVKPSETLSLTCVSGVSLPDYGVSWIRQPPGKCLEWIGVIWGS FTTYQSSLKSRVTISKDNNSKNQVSLKLSSVTAADTAVVYCAKHYYGGSYAMDY WGQGTLVTVSSGGGSDIQMTQSPSSLASVGDRVITCRASQISSYLNWY <u>QKPGKAPKLLIYAASSLQSGVPSRESGSGSGTDFTLTISLQPEDFATYYC</u> <u>QOSYSTPLTFGCGTKVEIKGGGGSGGGGGGGSGGGSEVQLLQESGGGL</u> <u>VQPGGSLRLSCAASGFTFSSYAMSWSVRQAPGKGLEWVSAISGSGGSTYYA</u> <u>DSVKGRFTISRDNSKNTLYLQMNLSRAEDTAVVYCARREWGEWSWLFDY</u> <u>WGQGTLVTVSSGGGSEIVMTQSPATLSLSPGERATLSCRASODISKYLNWYQ</u> <u>QKPGQAPRLLIYHTSRLHSGTIPARFSGSGSGTDYTLTISSLQPEDFAVYFCQGN</u> <u>TLPYTFGCGTKLEIK</u>
SEQ ID NO: 347	JL9 full length diabody CAR	QVQLQESGPGLVKPSETLSLTCVSGVSLPDYGVSWIRQPPGKCLEWIGVI WGSETTYQSSLKSRVTISKDNNSKNQVSLKLSSVTAADTAVVYCAKHYYY GGSYAMDYWGQGTLVTVSSGGGSDIQMTQSPSSLASVGDRVITCRAS QSISSYLNWYQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISLQ PEDFATYYCQSYSTPLTFGCGTKVEIKGGGGSGGGGGGGSGGGSEV QLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWSVRQAPGKGLEWVSAIS GSGGSTYYADSVKGRFTISRDNSKNTLYLQMNLSRAEDTAVVYCARREW WGESWLFYWGQGTLVTVSSGGGSEIVMTQSPATLSLSPGERATLSCR SQDISKYLNWYQKPGQAPRLLIYHTSRLHSGTIPARFSGSGSGTDYTLTISSL QPEDFAVYFCQGNTLPYTFGCGTKLEIKTTTPAPRPTPA EACRPAAGGAHVTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKK LLYIFKQPFMRPVQTQEEDGCSRFPPEEEEGGCERVKFSRSADAPAYKQ GONQLYNELNLGRREEVYDVLDKRRGRDPEMGGKPRRNQEGLYNELQK DKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR
SEQ ID NO: 330	JL10 antigen binding domain	EVQLLESGGLVQPGGSLRLSCAASGFTFSSYAMSWSVRQAPGKCLEWVSA ISGSGGTTYYADSVKGRFTISRDNSKNTLYLQMNLSRAEDTAVVYCARRE WWGESWLFYWGQGTLVTVSSGGGSEIVMTQSPATLSLSPGERATLSCRAS QDISKYLNWYQKPGQAPRLLIYHTSRLHSGTIPARFSGSGSGTDYTLTISSLQ PEDFAVYFCQGNTLPYTFGCGTKLEIKGGGGSGGGGGGGGGGGGGGG SGPGLVKPSETLSLTCVSGVSLPDYGVSWIRQPPGKGLEWIGVIWGETTYQ SKRSRVITISKDNNSKNQVSLKLSSVTAADTAVVYCAKHYYGGSYAMDYWGQGTL VTVSSGGGSDIQMTQSPSSLASVGDRVITCRASQSISSYLNWYQKPGK APKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQSYSTP LTFGCGTKVEIK
SEQ ID NO: 348	JL10 full length diabody CAR	EVQLLESGGLVQPGGSLRLSCAASGFTFSSYAMSWSVRQAPGKCLEWVSA ISGSGGTTYYADSVKGRFTISRDNSKNTLYLQMNLSRAEDTAVVYCARRE WWGESWLFYWGQGTLVTVSSGGGSEIVMTQSPATLSLSPGERATLSCR ASQDISKYLNWYQKPGQAPRLLIYHTSRLHSGTIPARFSGSGSGTDYTLTIS SLQPEDFAVYFCQGNTLPYTFGCGTKLEIKGGGGSGGGGGGGGGGGGGGG SQVQLQESGPGLVKPSETLSLTCVSGVSLPDYGVSWIRQPPGKGLEWIGVI WGSETTYQSSLKSRVTISKDNNSKNQVSLKLSSVTAADTAVVYCAKHYYY GGSYAMDYWGQGTLVTVSSGGGSDIQMTQSPSSLASVGDRVITCRAS QSISSYLNWYQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISLQ PEDFATYYCQSYSTPLTFGCGTKVEIKTTTPAPRPTPA EACRPAAGGAHVTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKK

TABLE 31-continued

Exemplary components of diabody CARs.		
SEQ ID NO	Description	Amino acid sequence*
		<u>LYIFKQPFMMPVQTTQEEDGCSCRFPEEEEGGCELRVKF</u> SRA <u>DAPAYKQD</u> QNQLYNE <u>NLN</u> GRREEYDVL <u>KRRGRD</u> P <u>EMGGKPRRKNPQEGLY</u> NELQKD KMAEAYSEIGMKGERRRGKGHDGLY <u>QGLSTATKDTY</u> DALHM <u>QALPPR</u>
SEQ ID NO: 250	Anti-CD19 VH (CTL119)	<u>QVQLQESGPGLVKPSETLSLCTVSGVSLPDYGVSWI</u> R <u>QPPGKCLEWIVI</u> WGSETTYQQ <u>SSLKSRVTIS</u> KD <u>NSKNQVSLKLSSVTAADTAVYYCAKH</u> YYY GGSYAMDYWG <u>QGT</u> LTVSS
SEQ ID NO: 251	Anti-CD19 VL (CTL119)	EIVMTQS <u>PATL</u> SLSPGERATLSCRASQDIS <u>KYLNWYQQKPGQAPRLLIYHTS</u> RLHSGIPAR <u>FSGSGSGTDY</u> T <u>LTISSLQ</u> PEDFAVYFC <u>QQGNTLPYTFGQGT</u> KL EIK
SEQ ID NO: 331	Anti-CD19 VH (CTL119) variant	<u>QVQLQESGPGLVKPSETLSLCTVSGVSLPDYGVSWI</u> R <u>QPPGKCLEWIVI</u> WGSETTYQQ <u>SSLKSRVTIS</u> KD <u>NSKNQVSLKLSSVTAADTAVYYCAKH</u> YYY GGSYAMDYWG <u>QGT</u> LTVSS
SEQ ID NO: 332	Anti-CD19 VL (CTL119) variant	EIVMTQS <u>PATL</u> SLSPGERATLSCRASQDIS <u>KYLNWYQQKPGQAPRLLIYHTS</u> RLHSGIPAR <u>FSGSGSGTDY</u> T <u>LTISSLQ</u> PEDFAVYFC <u>QQGNTLPYTFGCGT</u> KL EIK
SEQ ID NO: 93	Anti-BCMA VH (PI61)	<u>QVQLQESGGVVQPGRS</u> RLSCAAS <u>GFTFSSYGMH</u> WVR <u>QAPGKGLEWVA</u> VISYDG <u>SNKYYADSVKGRFTI</u> SR <u>DNSKNTLYLQMNSLRAEDTAVYYCGGS</u> GYALHDDYY <u>GLDVWGQGT</u> LTVSS
SEQ ID NO: 102	Anti-BCMA VL (PI61)	QSALTQPASV <u>SGSPGQS</u> ITISCTGTSSDVGGNYVSWYQQHP <u>GKAPKLM</u> IY DVSNRP <u>SGVSNRFS</u> GS <u>KGNTASLTISGLQAED</u> DEYY <u>CSSYTSS</u> STLYVFG SGTKVTVL
SEQ ID NO: 333	Anti-BCMA VH (PI61) variant	<u>QVQLQESGGVVQPGRS</u> RLSCAAS <u>GFTFSSYGMH</u> WVR <u>QAPGKCLEWVA</u> VISYDG <u>SNKYYADSVKGRFTI</u> SR <u>DNSKNTLYLQMNSLRAEDTAVYYCGGS</u> GYALHDDYY <u>GLDVWGQGT</u> LTVSS
SEQ ID NO: 334	Anti-BCMA VL (PI61) variant	QSALTQPASV <u>SGSPGQS</u> ITISCTGTSSDVGGNYVSWYQQHP <u>GKAPKLM</u> IY DVSNRP <u>SGVSNRFS</u> GS <u>KGNTASLTISGLQAED</u> DEYY <u>CSSYTSS</u> STLYVFG CGTKVTVL
SEQ ID NO: 78	Anti-BCMA VH (R1G5)	<u>EVQLLES</u> GGGLVQ <u>PGGSL</u> RLSCAAS <u>GFTFSSYAMS</u> WVR <u>QAPGKGLEWVA</u> IS <u>QSGGST</u> TYYADSVKGRFTI <u>SRD</u> NSKNTLYLQMNSLRAEDTAVYYCARRE WWGE <u>SWLF</u> PDYWG <u>QGT</u> LTVSS
SEQ ID NO: 61	Anti-BCMA VL (R1G5)	DIQMTQS <u>PSSLS</u> ASVGDRVTITCRASQSISSYLNWYQQ <u>KPGKAPKLLIYAA</u> S SL <u>QSGVP</u> SR <u>FSGSGSGTDF</u> T <u>LTISSLQ</u> PEDFA <u>TYYCQQSY</u> STPL <u>TFGQGT</u> KVE IK
SEQ ID NO: 335	Anti-BCMA VH (R1G5) variant	<u>EVQLLES</u> GGGLVQ <u>PGGSL</u> RLSCAAS <u>GFTFSSYAMS</u> WVR <u>QAPGKCLEWVA</u> IS <u>QSGGST</u> TYYADSVKGRFTI <u>SRD</u> NSKNTLYLQMNSLRAEDTAVYYCARRE WWGE <u>SWLF</u> PDYWG <u>QGT</u> LTVSS
SEQ ID NO: 336	Anti-BCMA VL (R1G5) variant	DIQMTQS <u>PSSLS</u> ASVGDRVTITCRASQSISSYLNWYQQ <u>KPGKAPKLLIYAA</u> S SL <u>QSGVP</u> SR <u>FSGSGSGTDF</u> T <u>LTISSLQ</u> PEDFA <u>TYYCQQSY</u> STPL <u>TFGCGT</u> KVE IK
SEQ ID NO: 5	Linker	GGGGSGGGGS
SEQ ID NO: 63	Linker	GGGGSGGGGGGGGGGGGGGG

\*VH sequences are underlined and VL sequences are double-underlined. CD19-binding sequences (VH and VL) are shown in italic.

#### Chimeric TCR

In one aspect, the antibodies and antibody fragments of the present invention can be grafted to one or more constant domain of a T cell receptor ("TCR") chain, for example, a TCR alpha or TCR beta chain, to create a chimeric TCR. Without being bound by theory, it is believed that chimeric TCRs will signal through the TCR complex upon antigen binding. For example, a scFv as disclosed herein, can be grafted to the constant domain, e.g., at least a portion of the extracellular constant domain, the transmembrane domain

and the cytoplasmic domain, of a TCR chain, for example, the TCR alpha chain and/or the TCR beta chain. As another example, an antibody fragment, for example a VL domain as described herein, can be grafted to the constant domain of a TCR alpha chain, and an antibody fragment, for example a VH domain as described herein, can be grafted to the constant domain of a TCR beta chain (or alternatively, a VL domain may be grafted to the constant domain of the TCR beta chain and a VH domain may be grafted to a TCR alpha chain). As another example, the CDRs of an antibody or

antibody fragment, e.g., the CDRs of an antibody or antibody fragment as described herein may be grafted into a TCR alpha and/or beta chain to create a chimeric TCR. For example, the LCDRs disclosed herein may be grafted into the variable domain of a TCR alpha chain and the HCDRs disclosed herein may be grafted to the variable domain of a TCR beta chain, or vice versa. Such chimeric TCRs may be produced by methods known in the art (For example, Willemsen R A et al, Gene Therapy 2000; 7: 1369-1377; Zhang T et al, Cancer Gene Ther 2004; 11: 487-496; Aggen et al, Gene Ther. 2012 April; 19(4):365-74).

#### Additional Embodiments

In one aspect, the CAR-expressing cell described herein can further comprise a second CAR, e.g., a second CAR that includes a different antigen binding domain, e.g., to the same target (BCMA) or a different target (e.g., CD19, CD20, or CS-1, or other multiple myeloma targets, e.g., kappa light chain, CD138, Lewis Y antigen, or CD38 (Garfall et al., Discovery Medicine, 2014, 17(91):37-46)). In one embodiment, the CAR-expressing cell comprises a first CAR that targets a first antigen and includes an intracellular signaling domain having a costimulatory signaling domain but not a primary signaling domain, and a second CAR that targets a second, different, antigen and includes an intracellular signaling domain having a primary signaling domain but not a costimulatory signaling domain. While not wishing to be bound by theory, placement of a costimulatory signaling domain, e.g., 4-1BB, CD28, CD27 ICOS, or OX-40, onto the first CAR, and the primary signaling domain, e.g., CD3 zeta, on the second CAR can limit the CAR activity to cells where both targets are expressed. In one embodiment, the CAR expressing cell comprises a first BCMA CAR that includes a BCMA binding domain, a transmembrane domain and a costimulatory domain and a second CAR that targets an antigen other than BCMA (e.g., an antigen expressed on leukemia or lymphoma cells, e.g., CD19, CD20, CS-1, kappa light chain, CD139, Lewis Y antigen, or CD38) and includes an antigen binding domain, a transmembrane domain and a primary signaling domain. In another embodiment, the CAR expressing cell comprises a first BCMA CAR that includes a BCMA binding domain, a transmembrane domain and a primary signaling domain and a second CAR that targets an antigen other than BCMA (e.g., an antigen expressed on leukemia or lymphoma cells, e.g., CD19, CD20, CS-1, kappa light chain, CD139, Lewis Y antigen, or CD38) and includes an antigen binding domain to the antigen, a transmembrane domain and a costimulatory signaling domain. In one embodiment, the CAR-expressing cell comprises a BCMA CAR described herein and a CAR that targets CD19 (CD19 CAR).

In one embodiment, the CAR-expressing cell comprises a BCMA CAR described herein and an inhibitory CAR. In one embodiment, the inhibitory CAR comprises an antigen binding domain that binds an antigen found on normal cells but not cancer cells. In one embodiment, the inhibitory CAR comprises the antigen binding domain, a transmembrane domain and an intracellular domain of an inhibitory molecule. For example, the intracellular domain of the inhibitory CAR can be an intracellular domain of PD1, PD-L1, PD-L2, CTLA4, TIM3, CEACAM (e.g., CEACAM-1, CEACAM-3 and/or CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 or CD270), KIR, A2aR, MHC class I, MHC class II, GAL9, adenosine, and TGFR beta.

In one embodiment, when the CAR-expressing cell comprises two or more different CARs, the antigen binding domains of the different CARs can be such that the antigen binding domains do not interact with one another. For example, a cell expressing a first and second CAR can have an antigen binding domain of the first CAR, e.g., as a fragment, e.g., an scFv, that does not form an association with the antigen binding domain of the second CAR, e.g., the antigen binding domain of the second CAR is a VH.

In some embodiments, the antigen binding domain comprises a single domain antigen binding (SDAB) molecules include molecules whose complementary determining regions are part of a single domain polypeptide. Examples include, but are not limited to, heavy chain variable domains, binding molecules naturally devoid of light chains, single domains derived from conventional 4-chain antibodies, engineered domains and single domain scaffolds other than those derived from antibodies.

SDAB molecules may be any of the art, or any future single domain molecules. SDAB molecules may be derived from any species including, but not limited to mouse, human, camel, llama, lamprey, fish, shark, goat, rabbit, and bovine. This term also includes naturally occurring single domain antibody molecules from species other than Camelidae and sharks.

In one aspect, an SDAB molecule can be derived from a variable region of the immunoglobulin found in fish, such as, for example, that which is derived from the immunoglobulin isotype known as Novel Antigen Receptor (NAR) found in the serum of shark. Methods of producing single domain molecules derived from a variable region of NAR ("IgNARs") are described in WO 03/014161 and Streltsov (2005) Protein Sci. 14:2901-2909.

According to another aspect, an SDAB molecule is a naturally occurring single domain antigen binding molecule known as heavy chain devoid of light chains. Such single domain molecules are disclosed in WO 9404678 and Hamers-Casterman, C. et al. (1993) Nature 363:446-448, for example. For clarity reasons, this variable domain derived from a heavy chain molecule naturally devoid of light chain is known herein as a VH or nanobody to distinguish it from the conventional VH of four chain immunoglobulins. Such a VH molecule can be derived from Camelidae species, for example in camel, llama, dromedary, alpaca and guanaco. Other species besides Camelidae may produce heavy chain molecules naturally devoid of light chain; such VHs are within the scope of the invention.

The SDAB molecules can be recombinant, CDR-grafted, humanized, camelized, de-immunized and/or in vitro generated (e.g., selected by phage display).

It has also been discovered that cells having a plurality of chimeric membrane embedded receptors comprising an antigen binding domain that interactions between the antigen binding domain of the receptors can be undesirable, e.g., because it inhibits the ability of one or more of the antigen binding domains to bind its cognate antigen. Accordingly, disclosed herein are cells having a first and a second non-naturally occurring chimeric membrane embedded receptor comprising antigen binding domains that minimize such interactions. Also disclosed herein are nucleic acids encoding a first and a second non-naturally occurring chimeric membrane embedded receptor comprising antigen binding domains that minimize such interactions, as well as methods of making and using such cells and nucleic acids. In an embodiment the antigen binding domain of one of said first said second non-naturally occurring chimeric membrane embedded receptor, comprises an scFv, and the other

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comprises a single VH domain, e.g., a camelid, shark, or lamprey single VH domain, or a single VH domain derived from a human or mouse sequence.

In some embodiments, the claimed invention comprises a first and second CAR, wherein the antigen binding domain of one of said first CAR said second CAR does not comprise a variable light domain and a variable heavy domain. In some embodiments, the antigen binding domain of one of said first CAR said second CAR is an scFv, and the other is not an scFv. In some embodiments, the antigen binding domain of one of said first CAR said second CAR comprises a single VH domain, e.g., a camelid, shark, or lamprey single VH domain, or a single VH domain derived from a human or mouse sequence. In some embodiments, the antigen binding domain of one of said first CAR said second CAR comprises a nanobody. In some embodiments, the antigen binding domain of one of said first CAR said second CAR comprises a camelid VHH domain.

In some embodiments, the antigen binding domain of one of said first CAR said second CAR comprises an scFv, and the other comprises a single VH domain, e.g., a camelid, shark, or lamprey single VH domain, or a single VH domain derived from a human or mouse sequence. In some embodiments, the antigen binding domain of one of said first CAR said second CAR comprises an scFv, and the other comprises a nanobody. In some embodiments, the antigen binding domain of one of said first CAR said second CAR comprises an scFv, and the other comprises a camelid VHH domain.

In some embodiments, when present on the surface of a cell, binding of the antigen binding domain of said first CAR to its cognate antigen is not substantially reduced by the presence of said second CAR. In some embodiments, binding of the antigen binding domain of said first CAR to its cognate antigen in the presence of said second CAR is 85%, 90%, 95%, 96%, 97%, 98% or 99% of binding of the antigen binding domain of said first CAR to its cognate antigen in the absence of said second CAR.

In some embodiments, when present on the surface of a cell, the antigen binding domains of said first CAR said second CAR, associate with one another less than if both were scFv antigen binding domains. In some embodiments, the antigen binding domains of said first CAR said second CAR, associate with one another 85%, 90%, 95%, 96%, 97%, 98% or 99% less than if both were scFv antigen binding domains.

In another aspect, the CAR-expressing cell described herein can further express another agent, e.g., an agent which enhances the activity of a CAR-expressing cell. For example, in one embodiment, the agent can be an agent which inhibits an inhibitory molecule, e.g., an agent described herein. Inhibitory molecules, e.g., PD1, can, in some embodiments, decrease the ability of a CAR-expressing cell to mount an immune effector response. Examples of inhibitory molecules include PD1, PD-L1, PD-L2, CTLA4, TIM3, CEACAM (e.g., CEACAM-1, CEACAM-3 and/or CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 or CD270), KIR, A2aR, MHC class I, MHC class II, GAL9, adenosine, and TGFR beta. In one embodiment, the agent which inhibits an inhibitory molecule comprises a first polypeptide, e.g., an inhibitory molecule, associated with a second polypeptide that provides a positive signal to the cell, e.g., an intracellular signaling domain described herein. In one embodiment, the agent comprises a first polypeptide, e.g., of an inhibitory molecule such as PD1, PD-L1, PD-L2, CTLA4, TIM3,

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CEACAM (e.g., CEACAM-1, CEACAM-3 and/or CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 or CD270), KIR, A2aR, MHC class I, MHC class II, GAL9, adenosine, and TGFR beta, or a fragment of any of these (e.g., at least a portion of an extracellular domain of any of these), and a second polypeptide which is an intracellular signaling domain described herein (e.g., comprising a costimulatory domain (e.g., 41BB, CD27 ICOS, or CD28, e.g., as described herein) and/or a primary signaling domain (e.g., a CD3 zeta signaling domain described herein). In one embodiment, the agent comprises a first polypeptide of PD1 or a fragment thereof (e.g., at least a portion of an extracellular domain of PD1), and a second polypeptide of an intracellular signaling domain described herein (e.g., a CD28 signaling domain described herein and/or a CD3 zeta signaling domain described herein). In embodiments, the CAR-expressing cell described herein comprises a switch costimulatory receptor, e.g., as described in WO 2013/019615, which is incorporated herein by reference in its entirety. PD1 is an inhibitory member of the CD28 family of receptors that also includes CD28, CTLA-4, ICOS, and BTLA. PD-1 is expressed on activated B cells, T cells and myeloid cells (Agata et al. 1996 Int. Immunol 8:765-75). Two ligands for PD1, PD-L1 and PD-L2 have been shown to downregulate T cell activation upon binding to PD1 (Freeman et al. 2000 J Exp Med 192:1027-34; Latchman et al. 2001 Nat Immunol 2:261-8; Carter et al. 2002 Eur J Immunol 32:634-43). PD-L1 is abundant in human cancers (Dong et al. 2003 J Mol Med 81:281-7; Blank et al. 2005 Cancer Immunol. Immunother 54:307-314; Konishi et al. 2004 Clin Cancer Res 10:5094). Immune suppression can be reversed by inhibiting the local interaction of PD1 with PD-L1.

In one embodiment, the agent comprises the extracellular domain (ECD) of an inhibitory molecule, e.g., Programmed Death 1 (PD1), can be fused to a transmembrane domain and intracellular signaling domains such as 41BB and CD3 zeta (also referred to herein as a PD1 CAR). In one embodiment, the PD1 CAR, when used in combinations with a BCMA CAR described herein, improves the persistence of the CAR-expressing cell, e.g., T cell or NK cell. In one embodiment, the CAR is a PD1 CAR comprising the extracellular domain of PD1 indicated as underlined in SEQ ID NO: 24. In one embodiment, the PD1 CAR comprises the amino acid sequence of SEQ ID NO: 24.

In one embodiment, the PD1 CAR comprises the amino acid sequence provided below (SEQ ID NO: 22).

In one embodiment, the agent comprises a nucleic acid sequence encoding the PD1 CAR, e.g., the PD1 CAR described herein. In one embodiment, the nucleic acid sequence for the PD1 CAR is provided as SEQ ID NO: 23, with the PD1 ECD underlined.

In another aspect, the present invention provides a population of CAR-expressing cells, e.g., CART cells or CAR-expressing NK cells. In some embodiments, the population of CAR-expressing cells comprises a mixture of cells expressing different CARs. For example, in one embodiment, the population of CAR-expressing cells (e.g., CART cells or CAR-expressing NK cells) can include a first cell expressing a CAR having an anti-BCMA binding domain described herein, and a second cell expressing a CAR having a different anti-BCMA binding domain, e.g., an anti-BCMA binding domain described herein that differs from the anti-BCMA binding domain in the CAR expressed by the first cell. As another example, the population of CAR-expressing cells can include a first cell expressing a CAR that includes

an anti-BCMA binding domain, e.g., as described herein, and a second cell expressing a CAR that includes an antigen binding domain to a target other than BCMA (e.g., CD19, CD20, CS-1, kappa light chain, CD139, Lewis Y antigen, or CD38). In one embodiment, the population of CAR-expressing cells includes a first cell expressing a CAR comprising an anti-BCMA binding domain, e.g., as described herein, and a second cell expressing a CAR comprising an antigen binding domain that targets CD19 (CD19 CAR). In one embodiment, the population of CAR-expressing cells includes, e.g., a first cell expressing a CAR that includes a primary intracellular signaling domain, and a second cell expressing a CAR that includes a secondary signaling domain.

In another aspect, the present invention provides a population of cells wherein at least one cell in the population expresses a CAR having an anti-BCMA domain described herein, and a second cell expressing another agent, e.g., an agent which enhances the activity of a CAR-expressing cell. For example, in one embodiment, the agent can be an agent which inhibits an inhibitory molecule.

Inhibitory molecules, e.g., can, in some embodiments, decrease the ability of a CAR-expressing cell to mount an immune effector response. Examples of inhibitory molecules include PD1, PD-L1, PD-L2, CTLA4, TIM3, CEACAM (e.g., CEACAM-1, CEACAM-3 and/or CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 or CD270), KIR, A2aR, MHC class I, MHC class II, GAL9, adenosine, and TGFR beta.

In one embodiment, the agent which inhibits an inhibitory molecule comprises a first polypeptide, e.g., an inhibitory molecule, associated with a second polypeptide that provides a positive signal to the cell, e.g., an intracellular signaling domain described herein. In one embodiment, the agent comprises a first polypeptide, e.g., of an inhibitory molecule such as PD1, PD-L1, PD-L2, CTLA4, TIM3, CEACAM (e.g., CEACAM-1, CEACAM-3 and/or CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 or CD270), KIR, A2aR, MHC class I, MHC class II, GAL9, adenosine, and TGFR beta, or a fragment of any of these (e.g., at least a portion of an extracellular domain of any of these), and a second polypeptide which is an intracellular signaling domain described herein (e.g., comprising a costimulatory domain (e.g., 41BB, CD27, ICOS, or CD28, e.g., as described herein) and/or a primary signaling domain (e.g., a CD3 zeta signaling domain described herein)). In one embodiment, the agent comprises a first polypeptide of PD1 or a fragment thereof (e.g., at least a portion of the extracellular domain of PD1), and a second polypeptide of an intracellular signaling domain described herein (e.g., a CD28 signaling domain described herein and/or a CD3 zeta signaling domain described herein).

In one aspect, the present invention provides methods comprising administering a population of CAR-expressing cells (e.g., CART cells or CAR-expressing NK cells), e.g., a mixture of cells expressing different CARs, in combination with another agent, e.g., a kinase inhibitor, such as a kinase inhibitor described herein. In another aspect, the present invention provides methods comprising administering a population of cells wherein at least one cell in the population expresses a CAR having an anti-cancer associated antigen binding domain as described herein, and a second cell expressing another agent, e.g., an agent which enhances the

activity of a CAR-expressing cell, in combination with another agent, e.g., a kinase inhibitor, such as a kinase inhibitor described herein.

#### Natural Killer Cell Receptor (NKR) CARs

In an embodiment, the CAR molecule described herein comprises one or more components of a natural killer cell receptor (NKR), thereby forming an NKR-CAR. The NKR component can be a transmembrane domain, a hinge domain, or a cytoplasmic domain from any of the following natural killer cell receptors: killer cell immunoglobulin-like receptor (KIR), e.g., KIR2DL1, KIR2DL2/L3, KIR2DL4, KIR2DL5A, KIR2DL5B, KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS4, DIR2DS5, KIR3DL1/S1, KIR3DL2, KIR3DL3, KIR2DP1, and KIR3DP1; natural cytotoxicity receptor (NCR), e.g., NKp30, NKp44, NKp46; signaling lymphocyte activation molecule (SLAM) family of immune cell receptors, e.g., CD48, CD229, 2B4, CD84, NTB-A, CRACC, BLAME, and CD2F-10; Fc receptor (FcR), e.g., CD16, and CD64; and Ly49 receptors, e.g., LY49A, LY49C. The NKR-CAR molecules described herein may interact with an adaptor molecule or intracellular signaling domain, e.g., DAP12. Exemplary configurations and sequences of CAR molecules comprising NKR components are described in International Publication No. WO2014/145252, the contents of which are hereby incorporated by reference.

#### Non-Antibody Scaffolds

In embodiments, the antigen binding domain comprises a non-antibody scaffold, for example, a fibronectin, ankyrin, domain antibody, lipocalin, small modular immuno-pharmaceutical, maxybody, Protein A, or affilin. The non-antibody scaffold has the ability to bind to target antigen on a cell. In embodiments, the antigen binding domain is a polypeptide or fragment thereof of a naturally occurring protein expressed on a cell. In some embodiments, the antigen binding domain comprises a non-antibody scaffold. A wide variety of non-antibody scaffolds can be employed so long as the resulting polypeptide includes at least one binding region which specifically binds to the target antigen on a target cell.

Non-antibody scaffolds include: fibronectin (Novartis, MA), ankyrin (Molecular Partners AG, Zurich, Switzerland), domain antibodies (Domantis, Ltd., Cambridge, MA, and Ablynx nv, Zwijnaarde, Belgium), lipocalin (Pieris Proteolab AG, Freising, Germany), small modular immuno-pharmaceuticals (Trubion Pharmaceuticals Inc., Seattle, WA), maxybodies (Avidia, Inc., Mountain View, CA), Protein A (Affibody AG, Sweden), and affilin (gamma-crystallin or ubiquitin) (Scil Proteins GmbH, Halle, Germany).

#### Strategies for Regulating Chimeric Antigen Receptors

There are many ways CAR activities can be regulated. In some embodiments, a regulatable CAR (RCAR) where the CAR activity can be controlled is desirable to optimize the safety and efficacy of a CAR therapy. For example, inducing apoptosis using, e.g., a caspase fused to a dimerization domain (see, e.g., Di et al., *N Engl. J. Med.* 2011 Nov. 3; 365(18):1673-1683), can be used as a safety switch in the CAR therapy of the instant invention. In another example, CAR-expressing cells can also express an inducible Caspase-9 (iCaspase-9) molecule that, upon administration of a dimerizer drug (e.g., rimiducid (also called AP1903 (Bellicum Pharmaceuticals) or AP20187 (Ariad)) leads to activation of the Caspase-9 and apoptosis of the cells. The iCaspase-9 molecule contains a chemical inducer of dimerization (CID) binding domain that mediates dimerization in the presence of a CID. This results in inducible and selective depletion of CAR-expressing cells. In some cases, the iCaspase-9 molecule is encoded by a nucleic acid

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molecule separate from the CAR-encoding vector(s). In some cases, the iCaspase-9 molecule is encoded by the same nucleic acid molecule as the CAR-encoding vector. The iCaspase-9 can provide a safety switch to avoid any toxicity of CAR-expressing cells. See, e.g., Song et al. Cancer Gene Ther. 2008; 15(10):667-75; Clinical Trial Id. No. NCT02107963; and Di Stasi et al. N. Engl. J. Med. 2011; 365:1673-83.

Alternative strategies for regulating the CAR therapy of the instant invention include utilizing small molecules or antibodies that deactivate or turn off CAR activity, e.g., by deleting CAR-expressing cells, e.g., by inducing antibody dependent cell-mediated cytotoxicity (ADCC). For example, CAR-expressing cells described herein may also express an antigen that is recognized by molecules capable of inducing cell death, e.g., ADCC or complement-induced cell death. For example, CAR expressing cells described herein may also express a receptor capable of being targeted by an antibody or antibody fragment. Examples of such receptors include EpCAM, VEGFR, integrins (e.g., integrins  $\alpha v\beta 3$ ,  $\alpha 4$ ,  $\alpha 1/\beta 3$ ,  $\alpha 4\beta 7$ ,  $\alpha 5\beta 1$ ,  $\alpha v\beta 3$ ,  $\alpha v$ ), members of the TNF receptor superfamily (e.g., TRAIL-R1, TRAIL-R2), PDGF Receptor, interferon receptor, folate receptor, GPNMB, ICAM-1, HLA-DR, CEA, CA-125, MUC1, TAG-72, IL-6 receptor, 5T4, GD2, GD3, CD2, CD3, CD4, CD5, CD11, CD11a/LFA-1, CD15, CD18/ITGB2, CD19, CD20, CD22, CD23/IgE Receptor, CD25, CD28, CD30, CD33, CD38, CD40, CD41, CD44, CD51, CD52, CD62L, CD74, CD80, CD125, CD147/basigin, CD152/CTLA-4, CD154/CD40L, CD195/CCR5, CD319/SLAMF7, and EGFR, and truncated versions thereof (e.g., versions preserving one or more extracellular epitopes but lacking one or more regions within the cytoplasmic domain). For example, CAR-expressing cells described herein may also express a truncated epidermal growth factor receptor (EGFR) which lacks signaling capacity but retains the epitope that is recognized by molecules capable of inducing ADCC, e.g., cetuximab (ER-BITUX<sup>®</sup>), such that administration of cetuximab induces ADCC and subsequent depletion of the CAR-expressing cells (see, e.g., WO2011/056894, and Jonnalagadda et al., Gene Ther. 2013; 20(8):853-860). Another strategy includes expressing a highly compact marker/suicide gene that combines target epitopes from both CD32 and CD20 antigens in the CAR-expressing cells described herein, which binds rituximab, resulting in selective depletion of the CAR-expressing cells, e.g., by ADCC (see, e.g., Philip et al., Blood. 2014; 124(8):1277-1287). Other methods for depleting CAR-expressing cells described herein include administration of CAMPATH<sup>®</sup>, a monoclonal anti-CD52 antibody that selectively binds and targets mature lymphocytes, e.g., CAR-expressing cells, for destruction, e.g., by inducing ADCC. In other embodiments, CAR-expressing cells can be selectively targeted using a CAR ligand, e.g., an anti-idiotypic antibody. In some embodiments, the anti-idiotypic antibody can cause effector cell activity, e.g., ADCC or ADC activities, thereby reducing the number of CAR-expressing cells. In other embodiments, the CAR ligand, e.g., the anti-idiotypic antibody, can be coupled to an agent that induces cell killing, e.g., a toxin, thereby reducing the number of CAR-expressing cells. Alternatively, the CAR molecules themselves can be configured such that the activity can be regulated, e.g., turned on and off, as described below.

In some embodiments, a RCAR comprises a set of polypeptides, typically two in the simplest embodiments, in which the components of a standard CAR described herein, e.g., an antigen binding domain and an intracellular signal-

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ing domain, are partitioned on separate polypeptides or members. In some embodiments, the set of polypeptides include a dimerization switch that, upon the presence of a dimerization molecule, can couple the polypeptides to one another e.g., can couple an antigen binding domain to an intracellular signaling domain. Additional description and exemplary configurations of such regulatable CARs are provided herein and in International Publication No. WO 2015/090229, hereby incorporated by reference in its entirety.

In an embodiment, an RCAR comprises two polypeptides or members: 1) an intracellular signaling member comprising an intracellular signaling domain, e.g., a primary intracellular signaling domain described herein, and a first switch domain; 2) an antigen binding member comprising an antigen binding domain, e.g., that targets a tumor antigen described herein, as described herein and a second switch domain. Optionally, the RCAR comprises a transmembrane domain described herein. In an embodiment, a transmembrane domain can be disposed on the intracellular signaling member, on the antigen binding member, or on both. (Unless otherwise indicated, when members or elements of an RCAR are described herein, the order can be as provided, but other orders are included as well. In other words, in an embodiment, the order is as set out in the text, but in other embodiments, the order can be different. E.g., the order of elements on one side of a transmembrane region can be different from the example, e.g., the placement of a switch domain relative to a intracellular signaling domain can be different, e.g., reversed).

In an embodiment, the first and second switch domains can form an intracellular or an extracellular dimerization switch. In an embodiment, the dimerization switch can be a homodimerization switch, e.g., where the first and second switch domain are the same, or a heterodimerization switch, e.g., where the first and second switch domain are different from one another.

In embodiments, an RCAR can comprise a “multi switch.” A multi switch can comprise heterodimerization switch domains or homodimerization switch domains. A multi switch comprises a plurality of, e.g., 2, 3, 4, 5, 6, 7, 8, 9, or 10, switch domains, independently, on a first member, e.g., an antigen binding member, and a second member, e.g., an intracellular signaling member. In an embodiment, the first member can comprise a plurality of first switch domains, e.g., FKBP-based switch domains, and the second member can comprise a plurality of second switch domains, e.g., FRB-based switch domains. In an embodiment, the first member can comprise a first and a second switch domain, e.g., a FKBP-based switch domain and a FRB-based switch domain, and the second member can comprise a first and a second switch domain, e.g., a FKBP-based switch domain and a FRB-based switch domain.

In an embodiment, the intracellular signaling member comprises one or more intracellular signaling domains, e.g., a primary intracellular signaling domain and one or more costimulatory signaling domains.

In an embodiment, the antigen binding member may comprise one or more intracellular signaling domains, e.g., one or more costimulatory signaling domains. In an embodiment, the antigen binding member comprises a plurality, e.g., 2 or 3 costimulatory signaling domains described herein, e.g., selected from 4-1BB, CD28, CD27, ICOS, and OX40, and in embodiments, no primary intracellular signaling domain. In an embodiment, the antigen binding member comprises the following costimulatory signaling domains, from the extracellular to intracellular direction: 4-1BB-

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CD27; 4-1BB-CD27; CD27-4-1BB; 4-1BB-CD28; CD28-4-1BB; OX40-CD28; CD28-OX40; CD28-4-1BB; or 4-1BB-CD28. In such embodiments, the intracellular binding member comprises a CD3zeta domain. In one such embodiment the RCAR comprises (1) an antigen binding member comprising, an antigen binding domain, a transmembrane domain, and two costimulatory domains and a first switch domain; and (2) an intracellular signaling domain comprising a transmembrane domain or membrane tethering domain and at least one primary intracellular signaling domain, and a second switch domain.

An embodiment provides RCARs wherein the antigen binding member is not tethered to the surface of the CAR cell. This allows a cell having an intracellular signaling member to be conveniently paired with one or more antigen binding domains, without transforming the cell with a sequence that encodes the antigen binding member. In such embodiments, the RCAR comprises: 1) an intracellular signaling member comprising: a first switch domain, a transmembrane domain, an intracellular signaling domain, e.g., a primary intracellular signaling domain, and a first switch domain; and 2) an antigen binding member comprising: an antigen binding domain, and a second switch domain, wherein the antigen binding member does not comprise a transmembrane domain or membrane tethering domain, and, optionally, does not comprise an intracellular signaling domain. In some embodiments, the RCAR may further comprise 3) a second antigen binding member comprising: a second antigen binding domain, e.g., a second antigen binding domain that binds a different antigen than is bound by the antigen binding domain; and a second switch domain.

Also provided herein are RCARs wherein the antigen binding member comprises bispecific activation and targeting capacity. In this embodiment, the antigen binding member can comprise a plurality, e.g., 2, 3, 4, or 5 antigen binding domains, e.g., scFVs, wherein each antigen binding domain binds to a target antigen, e.g. different antigens or the same antigen, e.g., the same or different epitopes on the same antigen. In an embodiment, the plurality of antigen binding domains are in tandem, and optionally, a linker or hinge region is disposed between each of the antigen binding domains. Suitable linkers and hinge regions are described herein.

An embodiment provides RCARs having a configuration that allows switching of proliferation. In this embodiment, the RCAR comprises: 1) an intracellular signaling member comprising: optionally, a transmembrane domain or membrane tethering domain; one or more co-stimulatory signaling domain, e.g., selected from 4-1BB, CD28, CD27, ICOS, and OX40, and a switch domain; and 2) an antigen binding member comprising: an antigen binding domain, a transmembrane domain, and a primary intracellular signaling domain, e.g., a CD3zeta domain, wherein the antigen binding member does not comprise a switch domain, or does not comprise a switch domain that dimerizes with a switch domain on the intracellular signaling member. In an embodiment, the antigen binding member does not comprise a co-stimulatory signaling domain. In an embodiment, the intracellular signaling member comprises a switch domain from a homodimerization switch. In an embodiment, the intracellular signaling member comprises a first switch domain of a heterodimerization switch and the RCAR comprises a second intracellular signaling member which comprises a second switch domain of the heterodimerization switch. In such embodiments, the second intracellular signaling member comprises the same intracellular signaling

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domains as the intracellular signaling member. In an embodiment, the dimerization switch is intracellular. In an embodiment, the dimerization switch is extracellular.

In any of the RCAR configurations described here, the first and second switch domains comprise a FKBP-FRB based switch as described herein.

Also provided herein are cells comprising an RCAR described herein. Any cell that is engineered to express a RCAR can be used as a RCARX cell. In an embodiment the RCARX cell is a T cell, and is referred to as a RCART cell. In an embodiment the RCARX cell is an NK cell, and is referred to as a RCARN cell.

Also provided herein are nucleic acids and vectors comprising RCAR encoding sequences. Sequence encoding various elements of an RCAR can be disposed on the same nucleic acid molecule, e.g., the same plasmid or vector, e.g., viral vector, e.g., lentiviral vector. In an embodiment, (i) sequence encoding an antigen binding member and (ii) sequence encoding an intracellular signaling member, can be present on the same nucleic acid, e.g., vector. Production of the corresponding proteins can be achieved, e.g., by the use of separate promoters, or by the use of a bicistronic transcription product (which can result in the production of two proteins by cleavage of a single translation product or by the translation of two separate protein products). In an embodiment, a sequence encoding a cleavable peptide, e.g., a P2A or F2A sequence, is disposed between (i) and (ii). In an embodiment, a sequence encoding an IRES, e.g., an EMCV or EV71 IRES, is disposed between (i) and (ii). In these embodiments, (i) and (ii) are transcribed as a single RNA. In an embodiment, a first promoter is operably linked to (i) and a second promoter is operably linked to (ii), such that (i) and (ii) are transcribed as separate mRNAs.

Alternatively, the sequence encoding various elements of an RCAR can be disposed on the different nucleic acid molecules, e.g., different plasmids or vectors, e.g., viral vector, e.g., lentiviral vector. E.g., the (i) sequence encoding an antigen binding member can be present on a first nucleic acid, e.g., a first vector, and the (ii) sequence encoding an intracellular signaling member can be present on the second nucleic acid, e.g., the second vector.

Dimerization switches Dimerization switches can be non-covalent or covalent. In a non-covalent dimerization switch, the dimerization molecule promotes a non-covalent interaction between the switch domains. In a covalent dimerization switch, the dimerization molecule promotes a covalent interaction between the switch domains.

In an embodiment, the RCAR comprises a FKBP/FRAP, or FKBP/FRB-based dimerization switch. FKBP12 (FKBP, or FK506 binding protein) is an abundant cytoplasmic protein that serves as the initial intracellular target for the natural product immunosuppressive drug, rapamycin. Rapamycin binds to FKBP and to the large PI3K homolog FRAP (RAFT, mTOR). FRB is a 93 amino acid portion of FRAP, that is sufficient for binding the FKBP-rapamycin complex (Chen, J., Zheng, X. F., Brown, E. J. & Schreiber, S. L. (1995) *Identification of an 11-kDa FKBP12-rapamycin-binding domain within the 289-kDa FKBP12-rapamycin-associated protein and characterization of a critical serine residue*. Proc Natl Acad Sci USA 92: 4947-51.)

In embodiments, an FKBP/FRAP, e.g., an FKBP/FRB, based switch can use a dimerization molecule, e.g., rapamycin or a rapamycin analog.

An exemplary amino acid sequence of FKBP is as follows:

DVPDYASLGGPSSPKKKRKVSRGVQVETISP-  
GDGRTFPKRQQT  
CVVHYTGMLEDGKKFDSSRDRNPKFKMLGKQE-

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VIRGWEEGVAQM                   SVGQRAKLTISPDYAY-  
GATGHPGIIPPHATLVDVELLKLETSY (SEQ ID NO:  
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In embodiments, an FKBP switch domain can comprise a fragment of FKBP having the ability to bind with FRB, or a fragment or analog thereof, in the presence of rapamycin or a rapalog. In one embodiment, the FKBP switch domain comprises the amino acid sequence of:

VQVETISPGDGRTFPKRQTCVVHYTGMLEDGK-  
KFDSSRDRN                       KPFKFMLGKQEVR-  
GWEEGVAQMSVGQRAKLTISPDYAYGATGHP   GIIP-  
PHATLVDVELLKLETS (SEQ ID NO: 276)

The amino acid sequence of FRB is as follows:

ILWHEMWHEG LEEASRLYFG ERNVKGMEV LEP-  
LHAMMER GPQLKETS NQAYGRDLME AQEWCR-  
KYMK SGNVKDLTQA WDLYYHVFRR ISK (SEQ ID  
NO: 277)

"FKBP/FRAP, e.g., an FKBP/FRB, based switch" as that term is used herein, refers to a dimerization switch comprising: a first switch domain, which comprises an FKBP fragment or analog thereof having the ability to bind with FRB, or a fragment or analog thereof, in the presence of rapamycin or a rapalog, e.g., RAD001, and has at least 70, 75, 80, 85, 90, 95, 96, 97, 98, or 99% identity with, or differs by no more than 30, 25, 20, 15, 10, 5, 4, 3, 2, or 1 amino acid residues from, the FKBP sequence of SEQ ID NO: 275 or 276; and a second switch domain, which comprises an FRB fragment or analog thereof having the ability to bind with FRB, or a fragment or analog thereof, in the presence of rapamycin or a rapalog, and has at least 70, 75, 80, 85, 90, 95, 96, 97, 98, or 99% identity with, or differs by no more than 30, 25, 20, 15, 10, 5, 4, 3, 2, or 1 amino acid residues

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from, the FRB sequence of SEQ ID NO: 277. In an embodiment, a RCAR described herein comprises one switch domain comprises amino acid residues disclosed in SEQ ID NO: 275 (or SEQ ID NO: 276), and one switch domain comprises amino acid residues disclosed in SEQ ID NO: 277.

In embodiments, the FKBP/FRB dimerization switch comprises a modified FRB switch domain that exhibits altered, e.g., enhanced, complex formation between an FRB-based switch domain, e.g., the modified FRB switch domain, a FKBP-based switch domain, and the dimerization molecule, e.g., rapamycin or a rapalogue, e.g., RAD001. In an embodiment, the modified FRB switch domain comprises one or more mutations, e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10 or more, selected from mutations at amino acid position(s) L2031, E2032, S2035, R2036, F2039, G2040, T2098, W2101, D2102, Y2105, and F2108, where the wild-type amino acid is mutated to any other naturally-occurring amino acid. In an embodiment, a mutant FRB comprises a mutation at E2032, where E2032 is mutated to phenylalanine (E2032F), methionine (E2032M), arginine (E2032R), valine (E2032V), tyrosine (E2032Y), isoleucine (E2032I), e.g., SEQ ID NO: 278, or leucine (E2032L), e.g., SEQ ID NO: 279. In an embodiment, a mutant FRB comprises a mutation at T2098, where T2098 is mutated to phenylalanine (T2098F) or leucine (T2098L), e.g., SEQ ID NO: 280. In an embodiment, a mutant FRB comprises a mutation at E2032 and at T2098, where E2032 is mutated to any amino acid, and where T2098 is mutated to any amino acid, e.g., SEQ ID NO: 281. In an embodiment, a mutant FRB comprises an E2032I and a T2098L mutation, e.g., SEQ ID NO: 282. In an embodiment, a mutant FRB comprises an E2032L and a T2098L mutation, e.g., SEQ ID NO: 283.

TABLE 18

Exemplary mutant FRB having increased affinity for a dimerization molecule.

FRB mutant	Amino Acid Sequence	SEQ ID NO:
E2032I mutant	ILWHEMWHEGLIEASRLYFGERNVKGMFEVLEPLHAMMERGPQLKE TSFNQAYGRDLMEAQEWCRKYMKSGNVKDLTQAWDLYHVERRISKTS	278
E2032L mutant	ILWHEMWHEGLIEASRLYFGERNVKGMFEVLEPLHAMMERGPQLKE TSFNQAYGRDLMEAQEWCRKYMKSGNVKDLIQAWDLYHVERRISKTS	279
T2098L mutant	ILWHEMWHEGLEEASRLYFGERNVKGMFEVLEPLHAMMERGPQLKE TSFNQAYGRDLMEAQEWCRKYMKSGNVKDLQQAWDLYHVERRISKTS	280
E2032, T2098 mutant	ILWHEMWHEGLXEASRLYFGERNVKGMFEVLEPLHAMMERGPQLKE TSFNQAYGRDLMEAQEWCRKYMKSGNVKDLXQAWDLYHVERRISKTS wherein X is any amino acid residue	281
E2032I, T2098L mutant	ILWHEMWHEGLIEASRLYFGERNVKGMFEVLEPLHAMMERGPQLKE TSFNQAYGRDLMEAQEWCRKYMKSGNVKDLIQAWDLYHVERRISKTS	282
E2032L, T2098L mutant	ILWHEMWHEGLIEASRLYFGERNVKGMFEVLEPLHAMMERGPQLKE TSFNQAYGRDLMEAQEWCRKYMKSGNVKDLQQAWDLYHVFRRISKTS	283

Other suitable dimerization switches include a GyrB-GyrB based dimerization switch, a Gibberellin-based dimerization switch, a tag/binder dimerization switch, and a halo-tag/snap-tag dimerization switch. Following the guidance provided herein, such switches and relevant dimerization molecules will be apparent to one of ordinary skill.

#### Dimerization Molecule

Association between the switch domains is promoted by the dimerization molecule. In the presence of dimerization molecule interaction or association between switch domains allows for signal transduction between a polypeptide asso-

ciated with, e.g., fused to, a first switch domain, and a polypeptide associated with, e.g., fused to, a second switch domain. In the presence of non-limiting levels of dimerization molecule signal transduction is increased by 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 5, 10, 50, 100 fold, e.g., as measured in a system described herein.

Rapamycin and rapamycin analogs (sometimes referred to as rapalogues), e.g., RAD001, can be used as dimerization molecules in a FKBP/FRB-based dimerization switch described herein. In an embodiment the dimerization molecule can be selected from rapamycin (sirolimus), RAD001

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(everolimus), zotarolimus, temsirolimus, AP-23573 (ridaforolimus), biolimus and AP21967. Additional rapamycin analogs suitable for use with FKBP/FRB-based dimerization switches are further described in the section entitled "Combination Therapies", or in the subsection entitled "Combination with a Low, Immune Enhancing, Dose of an mTOR inhibitor".

#### Split CAR

In some embodiments, the CAR-expressing cell uses a split CAR. The split CAR approach is described in more detail in publications WO2014/055442 and WO2014/055657, incorporated herein by reference. Briefly, a split CAR system comprises a cell expressing a first CAR having a first antigen binding domain and a costimulatory domain (e.g., 41BB), and the cell also expresses a second CAR having a second antigen binding domain and an intracellular signaling domain (e.g., CD3 zeta). When the cell encounters the first antigen, the costimulatory domain is activated, and the cell proliferates. When the cell encounters the second antigen, the intracellular signaling domain is activated and cell-killing activity begins. Thus, the CAR-expressing cell is only fully activated in the presence of both antigens. In embodiments the first antigen binding domain recognizes BCMA, e.g., comprises an antigen binding domain described herein, and the second antigen binding domain recognizes an antigen expressed on acute myeloid leukemia cells, e.g., CD123, CLL-1, CD34, FLT3, or folate receptor beta. In embodiments the first antigen binding domain recognizes BCMA, e.g., comprises an antigen binding domain described herein, and the second antigen binding domain recognizes an antigen expressed on B-cells, e.g., CD10, CD19, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, or CD79a.

#### Co-Expression of CAR with Other Molecules or Agents

#### Co-Expression of a Second CAR

In some embodiments, the CAR-expressing cell described herein can further comprise a second CAR, for example, a second CAR that includes a different antigen binding domain, for example, to the same target (for example, CD19) or a different target (for example, a target other than CD19, for example, a target described herein). In some embodiments, the CAR-expressing cell comprises a first CAR that targets a first antigen and includes an intracellular signaling domain having a costimulatory signaling domain but not a primary signaling domain, and a second CAR that targets a second, different, antigen and includes an intracellular signaling domain having a primary signaling domain but not a costimulatory signaling domain. Placement of a costimulatory signaling domain, for example, 4-1BB, CD28, CD27, OX-40 or ICOS, onto the first CAR, and the primary signaling domain, for example, CD3 zeta, on the second CAR can limit the CAR activity to cells where both targets are expressed. In some embodiments, the CAR expressing cell comprises a first CAR that includes an antigen binding domain, a transmembrane domain and a costimulatory domain and a second CAR that targets another antigen and includes an antigen binding domain, a transmembrane domain and a primary signaling domain. In some embodiments, the CAR expressing cell comprises a first CAR that includes an antigen binding domain, a transmembrane domain and a primary signaling domain and a second CAR that targets another antigen and includes an antigen binding domain to the antigen, a transmembrane domain and a costimulatory signaling domain.

In some embodiments, the CAR-expressing cell comprises an XCAR described herein and an inhibitory CAR. In some embodiments, the inhibitory CAR comprises an anti-

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gen binding domain that binds an antigen found on normal cells but not cancer cells, for example, normal cells that also express X. In some embodiments, the inhibitory CAR comprises the antigen binding domain, a transmembrane domain and an intracellular domain of an inhibitory molecule. For example, the intracellular domain of the inhibitory CAR can be an intracellular domain of PD1, PD-L1, PD-L2, CTLA4, TIM3, CEACAM (CEACAM-1, CEACAM-3, and/or CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 or CD270), KIR, A2aR, MHC class I, MHC class II, GAL9, adenosine, and TGF (for example, TGF beta).

In some embodiments, when the CAR-expressing cell comprises two or more different CARs, the antigen binding domains of the different CARs can be such that the antigen binding domains do not interact with one another. For example, a cell expressing a first and second CAR can have an antigen binding domain of the first CAR, for example, as a fragment, for example, an scFv, that does not form an association with the antigen binding domain of the second CAR, for example, the antigen binding domain of the second CAR is a VH.

In some embodiments, the antigen binding domain comprises a single domain antigen binding (SDAB) molecules include molecules whose complementary determining regions are part of a single domain polypeptide. Examples include, but are not limited to, heavy chain variable domains, binding molecules naturally devoid of light chains, single domains derived from conventional 4-chain antibodies, engineered domains and single domain scaffolds other than those derived from antibodies. SDAB molecules may be any of the art, or any future single domain molecules. SDAB molecules may be derived from any species including, but not limited to mouse, human, camel, llama, lamprey, fish, shark, goat, rabbit, and bovine. This term also includes naturally occurring single domain antibody molecules from species other than Camelidae and sharks.

In some embodiments, an SDAB molecule can be derived from a variable region of the immunoglobulin found in fish, such as, for example, that which is derived from the immunoglobulin isotype known as Novel Antigen Receptor (NAR) found in the serum of shark. Methods of producing single domain molecules derived from a variable region of NAR ("IgNARs") are described in WO 03/014161 and Streltsov (2005) Protein Sci. 14:2901-2909.

In some embodiments, an SDAB molecule is a naturally occurring single domain antigen binding molecule known as heavy chain devoid of light chains. Such single domain molecules are disclosed in WO 9404678 and Hamers-Casterman, C. et al. (1993) Nature 363:446-448, for example. For clarity reasons, this variable domain derived from a heavy chain molecule naturally devoid of light chain is known herein as a VH or nanobody to distinguish it from the conventional VH of four chain immunoglobulins. Such a VH molecule can be derived from Camelidae species, for example in camel, llama, dromedary, alpaca and guanaco. Other species besides Camelidae may produce heavy chain molecules naturally devoid of light chain; such VHs are within the scope of the invention.

The SDAB molecules can be recombinant, CDR-grafted, humanized, camelized, de-immunized and/or in vitro generated (for example, selected by phage display).

It has also been discovered, that cells having a plurality of chimeric membrane embedded receptors comprising an antigen binding domain that interactions between the antigen binding domain of the receptors can be undesirable, for

example, because it inhibits the ability of one or more of the antigen binding domains to bind its cognate antigen. Accordingly, disclosed herein are cells having a first and a second non-naturally occurring chimeric membrane embedded receptor comprising antigen binding domains that minimize such interactions. Also disclosed herein are nucleic acids encoding a first and a second non-naturally occurring chimeric membrane embedded receptor comprising an antigen binding domains that minimize such interactions, as well as methods of making and using such cells and nucleic acids. In some embodiments the antigen binding domain of one of the first and the second non-naturally occurring chimeric membrane embedded receptor, comprises an scFv, and the other comprises a single VH domain, for example, a camelid, shark, or lamprey single VH domain, or a single VH domain derived from a human or mouse sequence.

In some embodiments, a composition herein comprises a first and second CAR, wherein the antigen binding domain of one of the first and the second CAR does not comprise a variable light domain and a variable heavy domain. In some embodiments, the antigen binding domain of one of the first and the second CAR is an scFv, and the other is not an scFv. In some embodiments, the antigen binding domain of one of the first and the second CAR comprises a single VH domain, for example, a camelid, shark, or lamprey single VH domain, or a single VH domain derived from a human or mouse sequence. In some embodiments, the antigen binding domain of one of the first and the second CAR comprises a nanobody. In some embodiments, the antigen binding domain of one of the first and the second CAR comprises a camelid VHH domain.

In some embodiments, the antigen binding domain of one of the first and the second CAR comprises an scFv, and the other comprises a single VH domain, for example, a camelid, shark, or lamprey single VH domain, or a single VH domain derived from a human or mouse sequence. In some embodiments, the antigen binding domain of one of the first and the second CAR comprises an scFv, and the other comprises a nanobody. In some embodiments, the antigen binding domain of one of the first and the second CAR comprises an scFv, and the other comprises a camelid VHH domain.

In some embodiments, when present on the surface of a cell, binding of the antigen binding domain of the first CAR to its cognate antigen is not substantially reduced by the presence of the second CAR. In some embodiments, binding of the antigen binding domain of the first CAR to its cognate antigen in the presence of the second CAR is at least 85%, 90%, 95%, 96%, 97%, 98% or 99%, for example, 85%, 90%, 95%, 96%, 97%, 98% or 99% of binding of the antigen binding domain of the first CAR to its cognate antigen in the absence of the second CAR.

In some embodiments, when present on the surface of a cell, the antigen binding domains of the first and the second CAR, associate with one another less than if both were scFv antigen binding domains. In some embodiments, the antigen binding domains of the first and the second CAR, associate with one another at least 85%, 90%, 95%, 96%, 97%, 98% or 99% less than, for example, 85%, 90%, 95%, 96%, 97%, 98% or 99% less than if both were scFv antigen binding domains.

#### Co-Expression of an Agent that Enhances CAR Activity

In some embodiments, the CAR-expressing cell described herein can further express another agent, for example, an agent that enhances the activity or fitness of a CAR-expressing cell.

For example, in some embodiments, the agent can be an agent which inhibits a molecule that modulates or regulates, for example, inhibits, T cell function. In some embodiments, the molecule that modulates or regulates T cell function is an inhibitory molecule. Inhibitory molecules, for example, PD1, can, in some embodiments, decrease the ability of a CAR-expressing cell to mount an immune effector response. Examples of inhibitory molecules include PD1, PD-L1, CTLA4, TIM3, LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 or CD270), KIR, A2aR, MHC class I, MHC class II, GAL9, adenosine, or TGF beta.

In embodiments, an agent, for example, an inhibitory nucleic acid, for example, a dsRNA, for example, an siRNA or shRNA; or for example, an inhibitory protein or system, for example, a clustered regularly interspaced short palindromic repeats (CRISPR), a transcription-activator like effector nuclease (TALEN), or a zinc finger endonuclease (ZFN), for example, as described herein, can be used to inhibit expression of a molecule that modulates or regulates, for example, inhibits, T-cell function in the CAR-expressing cell. In some embodiments the agent is an shRNA, for example, an shRNA described herein. In some embodiments, the agent that modulates or regulates, for example, inhibits, T-cell function is inhibited within a CAR-expressing cell. For example, a dsRNA molecule that inhibits expression of a molecule that modulates or regulates, for example, inhibits, T-cell function is linked to the nucleic acid that encodes a component, for example, all of the components, of the CAR.

In some embodiments, the agent which inhibits an inhibitory molecule comprises a first polypeptide, for example, an inhibitory molecule, associated with a second polypeptide that provides a positive signal to the cell, for example, an intracellular signaling domain described herein. In some embodiments, the agent comprises a first polypeptide, for example, of an inhibitory molecule such as PD1, PD-L1, CTLA4, TIM3, LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 or CD270), KIR, A2aR, MHC class I, MHC class II, GAL9, adenosine, or TGF beta, or a fragment of any of these (for example, at least a portion of an extracellular domain of any of these), and a second polypeptide which is an intracellular signaling domain described herein (for example, comprising a costimulatory domain (for example, 41BB, CD27 or CD28, for example, as described herein) and/or a primary signaling domain (for example, a CD3 zeta signaling domain described herein). In some embodiments, the agent comprises a first polypeptide of PD1 or a fragment thereof (for example, at least a portion of an extracellular domain of PD1), and a second polypeptide of an intracellular signaling domain described herein (for example, a CD28 signaling domain described herein and/or a CD3 zeta signaling domain described herein). PD1 is an inhibitory member of the CD28 family of receptors that also includes CD28, CTLA-4, ICOS, and BTLA. PD-1 is expressed on activated B cells, T cells and myeloid cells (Agata et al. 1996 *Int. Immunol.* 8:765-75). Two ligands for PD1, PD-L1 and PD-L2 have been shown to downregulate T cell activation upon binding to PD1 (Freeman et al. 2000 *J Exp Med* 192:1027-34; Latchman et al. 2001 *Nat Immunol.* 2:261-8; Carter et al. 2002 *Eur J Immunol.* 32:634-43). PD-L1 is abundant in human cancers (Dong et al. 2003 *J Mol Med* 81:281-7; Blank et al. 2005 *Cancer Immunol. Immunother.* 54:307-314; Konishi et al. 2004 *Clin Cancer Res* 10:5094). Immune suppression can be reversed by inhibiting the local interaction of PD1 with PD-L1.

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In some embodiments, the agent comprises the extracellular domain (ECD) of an inhibitory molecule, for example, Programmed Death 1 (PD1), can be fused to a transmembrane domain and intracellular signaling domains such as 41BB and CD3 zeta (also referred to herein as a PD1 CAR). In some embodiments, the PD1 CAR, when used in combinations with an XCAR described herein, improves the persistence of the T cell. In some embodiments, the CAR is a PD1 CAR comprising the extracellular domain of PD1 indicated as underlined in SEQ ID NO: 24. In some embodiments, the PD1 CAR comprises the amino acid sequence of SEQ ID NO: 24.

In some embodiments, the PD1 CAR comprises the amino acid sequence of SEQ ID NO: 22.

In some embodiments, the agent comprises a nucleic acid sequence encoding the PD1 CAR, for example, the PD1 CAR described herein. In some embodiments, the nucleic acid sequence for the PD1 CAR is provided as SEQ ID NO: 23, with the PD1 ECD underlined.

In another example, in some embodiments, the agent which enhances the activity of a CAR-expressing cell can be a costimulatory molecule or costimulatory molecule ligand. Examples of costimulatory molecules include MHC class I molecule, BTLA and a Toll ligand receptor, as well as OX40, CD27, CD28, CDS, ICAM-1, LFA-1 (CD11a/CD18), ICOS (CD278), and 4-1BB (CD137). Further examples of such costimulatory molecules include CDS, ICAM-1, GITR, BAFFR, HVEM (LIGHTR), SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD160, CD19, CD4, CD8alpha, CD8beta, IL2R beta, IL2R gamma, IL7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, NKG2C, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMP4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMP6 (NTB-A, Ly108), SLAM (SLAMP1, CD150, IPO-3), BLAME (SLAMP8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, and a ligand that specifically binds with CD83., for example, as described herein. Examples of costimulatory molecule ligands include CD80, CD86, CD40L, ICOSL, CD70, OX40L, 4-1BBL, GITRL, and LIGHT. In embodiments, the costimulatory molecule ligand is a ligand for a costimulatory molecule different from the costimulatory molecule domain of the CAR. In embodiments, the costimulatory molecule ligand is a ligand for a costimulatory molecule that is the same as the costimulatory molecule domain of the CAR. In some embodiments, the costimulatory molecule ligand is 4-1BBL. In some embodiments, the costimulatory ligand is CD80 or CD86. In some embodiments, the costimulatory molecule ligand is CD70. In embodiments, a CAR-expressing immune effector cell described herein can be further engineered to express one or more additional costimulatory molecules or costimulatory molecule ligands.

**Co-expression of CAR with a Chemokine Receptor** In embodiments, the CAR-expressing cell described herein, for example, CD19 CAR-expressing cell, further comprises a chemokine receptor molecule. Transgenic expression of chemokine receptors CCR2b or CXCR2 in T cells enhances trafficking to CCL2- or CXCL1-secreting solid tumors including melanoma and neuroblastoma (Craddock et al., J Immunother. 2010 October; 33(8):780-8 and Kershaw et al., Hum Gene Ther. 2002 Nov. 1; 13(16):1971-80). Thus, without wishing to be bound by theory, it is believed that chemokine receptors expressed in CAR-expressing cells that

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recognize chemokines secreted by tumors, for example, solid tumors, can improve homing of the CAR-expressing cell to the tumor, facilitate the infiltration of the CAR-expressing cell to the tumor, and enhances antitumor efficacy of the CAR-expressing cell. The chemokine receptor molecule can comprise a naturally occurring or recombinant chemokine receptor or a chemokine-binding fragment thereof. A chemokine receptor molecule suitable for expression in a CAR-expressing cell (for example, CAR-Tx) described herein include a CXC chemokine receptor (for example, CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, CXCR6, or CXCR7), a CC chemokine receptor (for example, CCR1, CCR2, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, or CCR11), a CX3C chemokine receptor (for example, CX3CR1), a XC chemokine receptor (for example, XCR1), or a chemokine-binding fragment thereof. In some embodiments, the chemokine receptor molecule to be expressed with a CAR described herein is selected based on the chemokine(s) secreted by the tumor. In some embodiments, the CAR-expressing cell described herein further comprises, for example, expresses, a CCR2b receptor or a CXCR2 receptor. In some embodiments, the CAR described herein and the chemokine receptor molecule are on the same vector or are on two different vectors. In embodiments where the CAR described herein and the chemokine receptor molecule are on the same vector, the CAR and the chemokine receptor molecule are each under control of two different promoters or are under the control of the same promoter.

### 30 Nucleic Acid Constructs Encoding a CAR

The present invention also provides an immune effector cell, for example, made by a method described herein, that includes a nucleic acid molecule encoding one or more CAR constructs described herein. In some embodiments, the nucleic acid molecule is provided as a messenger RNA transcript. In some embodiments, the nucleic acid molecule is provided as a DNA construct.

The nucleic acid molecules described herein can be a DNA molecule, an RNA molecule, or a combination thereof. In some embodiments, the nucleic acid molecule is an mRNA encoding a CAR polypeptide as described herein. In other embodiments, the nucleic acid molecule is a vector that includes any of the aforesaid nucleic acid molecules.

In some embodiments, the antigen binding domain of a 45 CAR of the invention (for example, a scFv) is encoded by a nucleic acid molecule whose sequence has been codon optimized for expression in a mammalian cell. In some embodiments, entire CAR construct of the invention is encoded by a nucleic acid molecule whose entire sequence has been codon optimized for expression in a mammalian cell. Codon optimization refers to the discovery that the frequency of occurrence of synonymous codons (i.e., codons that code for the same amino acid) in coding DNA is biased in different species. Such codon degeneracy allows an identical polypeptide to be encoded by a variety of nucleotide sequences. A variety of codon optimization methods is known in the art, and include, for example, methods disclosed in at least U.S. Pat. Nos. 5,786,464 and 6,114,148.

Accordingly, in some embodiments, an immune effector cell, for example, made by a method described herein, includes a nucleic acid molecule encoding a chimeric antigen receptor (CAR), wherein the CAR comprises an antigen binding domain that binds to a tumor antigen described herein, a transmembrane domain (for example, a transmembrane domain described herein), and an intracellular signaling domain (for example, an intracellular signaling domain described herein) comprising a stimulatory domain, for

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example, a costimulatory signaling domain (for example, a costimulatory signaling domain described herein) and/or a primary signaling domain (for example, a primary signaling domain described herein, for example, a zeta chain described herein).

The present invention also provides vectors in which a nucleic acid molecule encoding a CAR, for example, a nucleic acid molecule described herein, is inserted. Vectors derived from retroviruses such as the lentivirus are suitable tools to achieve long-term gene transfer since they allow long-term, stable integration of a transgene and its propagation in daughter cells. Lentiviral vectors have the added advantage over vectors derived from onco-retroviruses such as murine leukemia viruses in that they can transduce non-proliferating cells, such as hepatocytes. They also have the added advantage of low immunogenicity. A retroviral vector may also be, for example, a gammaretroviral vector. A gammaretroviral vector may include, for example, a promoter, a packaging signal ( $\psi$ ), a primer binding site (PBS), one or more (for example, two) long terminal repeats (LTR), and a transgene of interest, for example, a gene encoding a CAR. A gammaretroviral vector may lack viral structural genes such as gag, pol, and env. Exemplary gammaretroviral vectors include Murine Leukemia Virus (MLV), Spleen-Focus Forming Virus (SFFV), and Myeloproliferative Sarcoma Virus (MPSV), and vectors derived therefrom. Other gammaretroviral vectors are described, for example, in Tobias Maetzig et al., "Gammaretroviral Vectors: Biology, Technology and Application" *Viruses*. 2011 June; 3(6): 677-713.

In some embodiments, the vector comprising the nucleic acid encoding the desired CAR is an adenoviral vector (A5/35). In some embodiments, the expression of nucleic acids encoding CARs can be accomplished using of transposons such as sleeping beauty, crispr, CAS9, and zinc finger nucleases. See below June et al. 2009 *Nature Reviews Immunology* 9.10: 704-716, is incorporated herein by reference.

In brief summary, the expression of natural or synthetic nucleic acids encoding CARs is typically achieved by operably linking a nucleic acid encoding the CAR polypeptide or portions thereof to a promoter and incorporating the construct into an expression vector. The vectors can be suitable for replication and integration eukaryotes. Typical cloning vectors contain transcription and translation terminators, initiation sequences, and promoters useful for regulation of the expression of the desired nucleic acid sequence.

The nucleic acid can be cloned into a number of types of vectors. For example, the nucleic acid can be cloned into a vector including, but not limited to a plasmid, a phagemid, a phage derivative, an animal virus, and a cosmid. Vectors of particular interest include expression vectors, replication vectors, probe generation vectors, and sequencing vectors.

Further, the expression vector may be provided to a cell in the form of a viral vector. Viral vector technology is well known in the art and is described, for example, in Sambrook et al., 2012, MOLECULAR CLONING: A LABORATORY MANUAL, volumes 1-4, Cold Spring Harbor Press, NY), and in other virology and molecular biology manuals. Viruses, which are useful as vectors include, but are not limited to, retroviruses, adenoviruses, adeno-associated viruses, herpes viruses, and lentiviruses. In general, a suitable vector contains an origin of replication functional in at least one organism, a promoter sequence, convenient restriction endonuclease sites, and one or more selectable markers, (for example, WO 01/96584; WO 01/29058; and U.S. Pat. No. 6,326,193).

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A number of viral based systems have been developed for gene transfer into mammalian cells. For example, retroviruses provide a convenient platform for gene delivery systems. A selected gene can be inserted into a vector and packaged in retroviral particles using techniques known in the art. The recombinant virus can then be isolated and delivered to cells of the subject either in vivo or ex vivo. A number of retroviral systems are known in the art. In some embodiments, adenovirus vectors are used.

10 A number of adenovirus vectors are known in the art. In some embodiments, lentivirus vectors are used. Additional promoter elements, for example, enhancers, regulate the frequency of transcriptional initiation. Typically, these are located in the region 30-110 bp upstream of the start site, although a number of promoters have been shown to contain functional elements downstream of the start site as well. The spacing between promoter elements frequently is flexible, so that promoter function is preserved when elements are 15 inverted or moved relative to one another. In the thymidine kinase (tk) promoter, the spacing between promoter elements can be increased to 50 bp apart before activity begins to decline. Depending on the promoter, it appears that individual elements can function either cooperatively or 20 independently to activate transcription. Exemplary promoters include the CMV IE gene, EF-1 $\alpha$ , ubiquitin C, or 25 phosphoglycerokinase (PGK) promoters.

An example of a promoter that is capable of expressing a 30 CAR encoding nucleic acid molecule in a mammalian T cell 35 is the EF1 $\alpha$  promoter. The native EF1 $\alpha$  promoter drives expression of the alpha subunit of the elongation factor-1 complex, which is responsible for the enzymatic delivery of aminoacyl tRNAs to the ribosome. The EF1 $\alpha$  promoter has been extensively used in mammalian expression plasmids and has been shown to be effective in driving CAR expression from nucleic acid molecules cloned into a lentiviral vector. See, for example, Milone et al., *Mol. Ther.* 17(8): 1453-1464 (2009). In some embodiments, the EF1 $\alpha$  promoter comprises the sequence provided in the Examples.

40 Another example of a promoter is the immediate early cytomegalovirus (CMV) promoter sequence. This promoter sequence is a strong constitutive promoter sequence capable of driving high levels of expression of any polynucleotide sequence operatively linked thereto. However, other constitutive promoter sequences may also be used, including, but not limited to the simian virus 40 (SV40) early promoter, mouse mammary tumor virus (MMTV), human immunodeficiency virus (HIV) long terminal repeat (LTR) promoter, MoMuLV promoter, an avian leukemia virus promoter, an Epstein-Barr virus immediate early promoter, a Rous sarcoma virus promoter, as well as human gene promoters such as, but not limited to, the actin promoter, the myosin promoter, the elongation factor-1 $\alpha$  promoter, the hemoglobin promoter, and the creatine kinase promoter. Further, the 45 invention should not be limited to the use of constitutive promoters. Inducible promoters are also contemplated as part of the invention. The use of an inducible promoter provides a molecular switch capable of turning on expression of the polynucleotide sequence which it is operatively linked when such expression is desired, or turning off the expression when expression is not desired. Examples of 50 inducible promoters include, but are not limited to a metallothionein promoter, a glucocorticoid promoter, a progesterone promoter, and a tetracycline promoter.

55 Another example of a promoter is the phosphoglycerate kinase (PGK) promoter. In embodiments, a truncated PGK promoter (for example, a PGK promoter with one or more,

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for example, 1, 2, 5, 10, 100, 200, 300, or 400, nucleotide deletions when compared to the wild-type PGK promoter sequence) may be desired.

The nucleotide sequences of exemplary PGK promoters are provided below.

WT PGK Promoter:

(SEQ ID NO: 190)  
 ACCCCTCTCCAGCCACTAACGCCAGTTGCTCCCTCGGCTGACGGCTGC  
 ACAGCAGGCCCTCGAACGTCTTACGCCCTGGCGCGCCCGTCTTGTC  
 CCGGGTGTGATGGCGGGGTGTGGGCGGAGGGCGTGGCGGGGAAGGGC  
 GCGACGAGAGCCGCGCGGGACGACTCGTCGGCGATAACCGGTGTC  
 TAGCGCCAGCCCGCGAACGTAACGAGGGACCGCGACAGGAGACGCTC  
 CCATGATCACTCTGCACGCCGAAGGCAAATAGTGCAGGCCGTGCGGC  
 TTGGCGTTCCCTGGAAGGGCTGAATCCCCGCTCGTCCTCGCAGCGGC  
 CCCCCGGGTGTTCCATGCCGCTCTAGGCCACTGCGACGCC  
 GCACCTTACACGCTCTGGGTCAGCCCGCGACGCC  
 GGTGCGGGTCTCGTCGGCGCAGGGACCGTTGGGTCGGACCGAACCT  
 TTTCCGCGTTGGGGTTGGGGCACCATAGCT

Exemplary truncated PGK Promoters:

PGK100:

ACCCCTCTCTCCAGC-  
 CACTAAGCCAGTTGCTCCCTCGGCTGACGGCT-  
 GCACGCGAG GCCTCCGAACGTCT-  
 TACGCCCTGTGGCGCGCCCGTCCTGTCCC  
 GTGATGGCGGGGT G (SEQ ID NO: 198)

PGK200:

ACCCCTCTCTCCAGC-  
 CACTAAGCCAGTTGCTCCCTCGGCTGACGGC-  
 TGACCGAG GCCTCCGAACGTCT-  
 TACGCCCTGTGGCGCGCCCGTCCTGTCCC  
 GTGATGGCGGGGT GTGGGGCG-  
 GAGGGCGTGGCGGG-  
 GAAGGGCCGGCAGCAGAGAGCCCGCGGGACG-  
 ACTCGT CGCGA-  
 TAACCGGTGTCGGGTAGCGCCAGCCCGCGACG-  
 GTAACG (SEQ ID NO: 191)

PGK300:

(SEQ ID NO: 192)  
 ACCCCTCTCCAGCCACTAACGCCAGTTGCTCCCTCGGCTGACGGCTGC  
 ACAGCAGGCCCTCGAACGTCTTACGCCCTGGCGCGCCCGTCTTGTC  
 CCGGGTGTGATGGCGGGGTGTGGGCGGAGGGCGTGGCGGGGAAGGGC  
 GCGACGAGAGCCGCGCGGGACGACTCGTCGGCGATAACCGGTGTC  
 TAGCGCCAGCCCGCGACGGTAACGAGGGACCGCGACAGGAGACGCTC  
 CCATGATCACTCTGCACGCCGAAGGCAAATAGTGCAGGCCGTGCGGC  
 TTGGCGTTCCCTGGAAGGGCTGAATCCCCG

PGK400:

(SEQ ID NO: 193)  
 ACCCCTCTCCAGCCACTAACGCCAGTTGCTCCCTCGGCTGACGGCTGC  
 ACAGCAGGCCCTCGAACGTCTTACGCCCTGGCGCGCCCGTCTTGTC  
 CCGGGTGTGATGGCGGGGTGTGGGCGGAGGGCGTGGCGGGGAAGGGC

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-continued

GGCGACGAGAGCCGCGCGGGACGACTCGTCGGCGATAACCGGTGTC  
 TAGCGCCAGCCGCGAACGTAACGAGGGACCGCGACAGGAGACGCTC  
 5 CCATGATCACTCTGCACGCCGAAGGCAAATAGTGCAGGCCGTGCGGC  
 TTGGCGTTCCCTGGAAGGGCTGAATCCCCGCTCGTCCTCGCAGCGGC  
 CCCCCGGGTGTTCCATGCCGCTCTAGGCCACTGCGACGCC  
 10 GCACTTCTACACGCTCTGGGTCAGCGC

A vector may also include, for example, a signal sequence to facilitate secretion, a polyadenylation signal and transcription terminator (for example, from Bovine Growth Hormone (BGH) gene), an element allowing episomal replication and replication in prokaryotes (for example SV40 origin and ColE1 or others known in the art) and/or elements to allow selection (for example, ampicillin resistance gene and/or zeocin marker).

In order to assess the expression of a CAR polypeptide or portions thereof, the expression vector to be introduced into a cell can also contain either a selectable marker gene or a reporter gene or both to facilitate identification and selection of expressing cells from the population of cells sought to be transfected or infected through viral vectors. In some embodiments, the selectable marker may be carried on a separate piece of DNA and used in a co-transfection procedure. Both selectable markers and reporter genes may be flanked with appropriate regulatory sequences to enable expression in the host cells. Useful selectable markers include, for example, antibiotic-resistance genes, such as neo and the like.

Reporter genes are used for identifying potentially transfected cells and for evaluating the functionality of regulatory sequences. In general, a reporter gene is a gene that is not present in or expressed by the recipient organism or tissue and that encodes a polypeptide whose expression is manifested by some easily detectable property, for example, enzymatic activity. Expression of the reporter gene is assayed at a suitable time after the DNA has been introduced into the recipient cells. Suitable reporter genes may include genes encoding luciferase, beta-galactosidase, chloramphenicol acetyl transferase, secreted alkaline phosphatase, or the green fluorescent protein gene (for example, Ui-Tei et al., 2000 FEBS Letters 479: 79-82). Suitable expression systems are well known and may be prepared using known techniques or obtained commercially. In general, the construct with the minimal 5' flanking region showing the highest level of expression of reporter gene is identified as the promoter. Such promoter regions may be linked to a reporter gene and used to evaluate agents for the ability to modulate promoter-driven transcription.

In embodiments, the vector may comprise two or more nucleic acid sequences encoding a CAR, for example, a CAR described herein, for example, a CD19 CAR, and a second CAR, for example, an inhibitory CAR or a CAR that specifically binds to an antigen other than CD19. In such embodiments, the two or more nucleic acid sequences encoding the CAR are encoded by a single nucleic molecule in the same frame and as a single polypeptide chain. In some embodiments, the two or more CARs, can, for example, be separated by one or more peptide cleavage sites. (for example, an auto-cleavage site or a substrate for an intracellular protease). Examples of peptide cleavage sites include T2A, P2A, E2A, or F2A sites.

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Methods of introducing and expressing genes into a cell are known in the art. In the context of an expression vector, the vector can be readily introduced into a host cell, for example, mammalian, bacterial, yeast, or insect cell by any method, for example, one known in the art. For example, the expression vector can be transferred into a host cell by physical, chemical, or biological means.

Physical methods for introducing a polynucleotide into a host cell include calcium phosphate precipitation, lipofection, particle bombardment, microinjection, electroporation, and the like. Methods for producing cells comprising vectors and/or exogenous nucleic acids are well-known in the art. See, for example, Sambrook et al., 2012, MOLECULAR CLONING: A LABORATORY MANUAL, volumes 1-4, Cold Spring Harbor Press, NY). A suitable method for the introduction of a polynucleotide into a host cell is calcium phosphate transfection.

Biological methods for introducing a polynucleotide of interest into a host cell include the use of DNA and RNA vectors. Viral vectors, and especially retroviral vectors, have become the most widely used method for inserting genes into mammalian, for example, human cells. Other viral vectors can be derived from lentivirus, poxviruses, herpes simplex virus 1, adenoviruses and adeno-associated viruses, and the like. See, for example, U.S. Pat. Nos. 5,350,674 and 5,585,362.

Chemical means for introducing a polynucleotide into a host cell include 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 (for example, an artificial membrane vesicle). Other methods of state-of-the-art targeted delivery of nucleic acids are available, such as delivery of polynucleotides with targeted nanoparticles or other suitable sub-micron sized delivery system.

In the case where a non-viral delivery system is utilized, an exemplary delivery vehicle is a liposome. The use of lipid formulations is contemplated for the introduction of the nucleic acids into a host cell (*in vitro*, *ex vivo* or *in vivo*). In some embodiments, the nucleic acid may be associated with a lipid. The nucleic acid associated with a lipid may be encapsulated in the aqueous interior of a liposome, interspersed within the lipid bilayer of a liposome, attached to a liposome via a linking molecule that is associated with both the liposome and the oligonucleotide, entrapped in a liposome, complexed with a liposome, dispersed in a solution containing a lipid, mixed with a lipid, combined with a lipid, contained as a suspension in a lipid, contained or complexed with a micelle, or otherwise associated with a lipid.

Lipid, lipid/DNA or lipid/expression vector associated compositions are not limited to any particular structure in solution. For example, they may be present in a bilayer structure, as micelles, or with a "collapsed" structure. They may also simply be interspersed in a solution, possibly forming aggregates that are not uniform in size or shape. Lipids are fatty substances which may be naturally occurring or synthetic lipids. For example, lipids include the fatty droplets that naturally occur in the cytoplasm as well as the class of compounds which contain long-chain aliphatic hydrocarbons and their derivatives, such as fatty acids, alcohols, amines, amino alcohols, and aldehydes.

Lipids suitable for use can be obtained from commercial sources. For example, dimyristyl phosphatidylcholine ("DMPC") can be obtained from Sigma, St. Louis, MO; dicetyl phosphate ("DCP") can be obtained from K & K

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Laboratories (Plainview, NY); cholesterol ("Choi") can be obtained from Calbiochem-Behring; dimyristyl phosphatidylglycerol ("DMPG") and other lipids may be obtained from Avanti Polar Lipids, Inc. (Birmingham, AL.). Stock solutions of lipids in chloroform or chloroform/methanol can be stored at about -20° C. Chloroform is used as the only solvent since it is more readily evaporated than methanol. "Liposome" is a generic term encompassing a variety of single and multilamellar lipid vehicles formed by the generation of enclosed lipid bilayers or aggregates. Liposomes can be characterized as having vesicular structures with a phospholipid bilayer membrane and an inner aqueous medium. Multilamellar liposomes have multiple lipid layers separated by aqueous medium. They form spontaneously when phospholipids are suspended in an excess of aqueous solution. The lipid components undergo self-rearrangement before the formation of closed structures and entrap water and dissolved solutes between the lipid bilayers (Ghosh et al., 1991 Glycobiology 5: 505-10). However, compositions that have different structures in solution than the normal vesicular structure are also encompassed. For example, the lipids may assume a micellar structure or merely exist as nonuniform aggregates of lipid molecules. Also contemplated are lipofectamine-nucleic acid complexes.

Regardless of the method used to introduce exogenous nucleic acids into a host cell or otherwise expose a cell to the inhibitor of the present invention, in order to confirm the presence of the recombinant nucleic acid sequence in the host cell, a variety of assays may be performed. Such assays include, for example, "molecular biological" assays well known to those of skill in the art, such as Southern and Northern blotting, RT-PCR and PCR; "biochemical" assays, such as detecting the presence or absence of a particular peptide, for example, by immunological means (ELISAs and Western blots) or by assays described herein to identify agents falling within the scope of the invention.

#### RNA Transfection

Disclosed herein are methods for producing an *in vitro* transcribed RNA CAR. RNA CAR and methods of using the same are described, for example, in paragraphs 553-570 of International Application WO2015/142675, filed Mar. 13, 2015, which is herein incorporated by reference in its entirety.

An immune effector cell can include a CAR encoded by a messenger RNA (mRNA). In some embodiments, the mRNA encoding a CAR described herein is introduced into an immune effector cell, for example, made by a method described herein, for production of a CAR-expressing cell.

In some embodiments, the *in vitro* transcribed RNA CAR can be introduced to a cell as a form of transient transfection. The RNA is produced by *in vitro* transcription using a polymerase chain reaction (PCR)-generated template. DNA of interest from any source can be directly converted by PCR into a template for *in vitro* mRNA synthesis using appropriate primers and RNA polymerase. The source of the DNA can be, for example, genomic DNA, plasmid DNA, phage DNA, cDNA, synthetic DNA sequence or any other appropriate source of DNA. The desired template for *in vitro* transcription is a CAR described herein. For example, the template for the RNA CAR comprises an extracellular region comprising a single chain variable domain of an antibody to a tumor associated antigen described herein; a hinge region (for example, a hinge region described herein), a transmembrane domain (for example, a transmembrane domain described herein such as a transmembrane domain of CD8a); and a cytoplasmic region that includes an intracellular signaling domain, for example, an intracellular

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signaling domain described herein, for example, comprising the signaling domain of CD3-zeta and the signaling domain of 4-1BB.

In some embodiments, the DNA to be used for PCR contains an open reading frame. The DNA can be from a naturally occurring DNA sequence from the genome of an organism. In some embodiments, the nucleic acid can include some or all of the 5' and/or 3' untranslated regions (UTRs). The nucleic acid can include exons and introns. In some embodiments, the DNA to be used for PCR is a human nucleic acid sequence. In some embodiments, the DNA to be used for PCR is a human nucleic acid sequence including the 5' and 3' UTRs. The DNA can alternatively be an artificial DNA sequence that is not normally expressed in a naturally occurring organism. An exemplary artificial DNA sequence is one that contains portions of genes that are ligated together to form an open reading frame that encodes a fusion protein. The portions of DNA that are ligated together can be from a single organism or from more than one organism.

PCR is used to generate a template for in vitro transcription of mRNA which is used for transfection. Methods for performing PCR are well known in the art. Primers for use in PCR are designed to have regions that are substantially complementary to regions of the DNA to be used as a template for the PCR. "Substantially complementary," as used herein, refers to sequences of nucleotides where a majority or all of the bases in the primer sequence are complementary, or one or more bases are non-complementary, or mismatched. Substantially complementary sequences are able to anneal or hybridize with the intended DNA target under annealing conditions used for PCR. The primers can be designed to be substantially complementary to any portion of the DNA template. For example, the primers can be designed to amplify the portion of a nucleic acid that is normally transcribed in cells (the open reading frame), including 5' and 3' UTRs. The primers can also be designed to amplify a portion of a nucleic acid that encodes a particular domain of interest. In some embodiments, the primers are designed to amplify the coding region of a human cDNA, including all or portions of the 5' and 3' UTRs. Primers useful for PCR can be generated by synthetic methods that are well known in the art. "Forward primers" are primers that contain a region of nucleotides that are substantially complementary to nucleotides on the DNA template that are upstream of the DNA sequence that is to be amplified. "Upstream" is used herein to refer to a location 5', to the DNA sequence to be amplified relative to the coding strand. "Reverse primers" are primers that contain a region of nucleotides that are substantially complementary to a double-stranded DNA template that are downstream of the DNA sequence that is to be amplified. "Downstream" is used herein to refer to a location 3' to the DNA sequence to be amplified relative to the coding strand.

Any DNA polymerase useful for PCR can be used in the methods disclosed herein. The reagents and polymerase are commercially available from a number of sources.

Chemical structures with the ability to promote stability and/or translation efficiency may also be used. The RNA in embodiments has 5' and 3' UTRs. In some embodiments, the 5' UTR is between one and 3000 nucleotides in length. The length of 5' and 3' UTR sequences to be added to the coding region can be altered by different methods, including, but not limited to, designing primers for PCR that anneal to different regions of the UTRs. Using this approach, one of ordinary skill in the art can modify the 5' and 3' UTR lengths required to achieve optimal translation efficiency following transfection of the transcribed RNA.

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The 5' and 3' UTRs can be the naturally occurring, endogenous 5' and 3' UTRs for the nucleic acid of interest. Alternatively, UTR sequences that are not endogenous to the nucleic acid of interest can be added by incorporating the 5' UTR sequences into the forward and reverse primers or by any other modifications of the template. The use of UTR sequences that are not endogenous to the nucleic acid of interest can be useful for modifying the stability and/or translation efficiency of the RNA. For example, it is known that AU-rich elements in 3' UTR sequences can decrease the stability of mRNA. Therefore, 3' UTRs can be selected or designed to increase the stability of the transcribed RNA based on properties of UTRs that are well known in the art.

In some embodiments, the 5' UTR can contain the Kozak sequence of the endogenous nucleic acid. Alternatively, when a 5' UTR that is not endogenous to the nucleic acid of interest is being added by PCR as described above, a consensus Kozak sequence can be redesigned by adding the 5' UTR sequence. Kozak sequences can increase the efficiency of translation of some RNA transcripts, but does not appear to be required for all RNAs to enable efficient translation. The requirement for Kozak sequences for many mRNAs is known in the art. In other embodiments the 5' UTR can be 5'UTR of an RNA virus whose RNA genome is stable in cells. In other embodiments various nucleotide analogues can be used in the 3' or 5' UTR to impede exonuclease degradation of the mRNA.

To enable synthesis of RNA from a DNA template without the need for gene cloning, a promoter of transcription should be attached to the DNA template upstream of the sequence to be transcribed. When a sequence that functions as a promoter for an RNA polymerase is added to the 5' end of the forward primer, the RNA polymerase promoter becomes incorporated into the PCR product upstream of the open reading frame that is to be transcribed. In some embodiments, the promoter is a T7 polymerase promoter, as described elsewhere herein. Other useful promoters include, but are not limited to, T3 and SP6 RNA polymerase promoters. Consensus nucleotide sequences for T7, T3 and SP6 promoters are known in the art.

In some embodiments, the mRNA has both a cap on the 5' end and a 3' poly(A) tail which determine ribosome binding, initiation of translation and stability mRNA in the cell. On a circular DNA template, for instance, plasmid DNA, RNA polymerase produces a long concatameric product which is not suitable for expression in eukaryotic cells. The transcription of plasmid DNA linearized at the end of the 3' UTR results in normal sized mRNA which is not effective in eukaryotic transfection even if it is polyadenylated after transcription.

On a linear DNA template, phage T7 RNA polymerase can extend the 3' end of the transcript beyond the last base of the template (Schenborn and Mierendorf, Nuc Acids Res., 13:6223-36 (1985); Nacheva and Berzal-Herranz, Eur. J. Biochem., 270:1485-65 (2003)).

The conventional method of integration of poly(A)/T stretches into a DNA template is molecular cloning. However, poly(A)/T sequence integrated into plasmid DNA can cause plasmid instability, which is why plasmid DNA templates obtained from bacterial cells are often highly contaminated with deletions and other aberrations. This makes cloning procedures not only laborious and time consuming but often not reliable. That is why a method which allows construction of DNA templates with poly(A)/T 3' stretch without cloning highly desirable.

The poly(A)/T segment of the transcriptional DNA template can be produced during PCR by using a reverse primer

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containing a polyT tail, such as 100T tail (SEQ ID NO: 31) (size can be 50-5000 T (SEQ ID NO: 32)), or after PCR by any other method, including, but not limited to, DNA ligation or in vitro recombination. Poly(A) tails also provide stability to RNAs and reduce their degradation. Generally, the length of a poly(A) tail positively correlates with the stability of the transcribed RNA. In some embodiments, the poly(A) tail is between 100 and 5000 adenosines (for example, SEQ ID NO: 33).

Poly(A) tails of RNAs can be further extended following in vitro transcription with the use of a poly(A) polymerase, such as *E. coli* poly(A) polymerase (E-PAP). In some embodiments, increasing the length of a poly(A) tail from 100 nucleotides to between 300 and 400 nucleotides (SEQ ID NO: 34) results in about a two-fold increase in the translation efficiency of the RNA. Additionally, the attachment of different chemical groups to the 3' end can increase mRNA stability. Such attachment can contain modified/artificial nucleotides, aptamers and other compounds. For example, ATP analogs can be incorporated into the poly(A) tail using poly(A) polymerase. ATP analogs can further increase the stability of the RNA. 5' caps can also provide stability to RNA molecules. In some embodiments, RNAs produced by the methods disclosed herein include a 5' cap. The 5' cap is provided using techniques known in the art and described herein (Cougot, et al., Trends in Biochem. Sci., 29:436-444 (2001); Stepinski, et al., RNA, 7:1468-95 (2001); Elango, et al., Biophys. Res. Commun., 330:958-966 (2005)).

The RNAs produced by the methods disclosed herein can also contain an internal ribosome entry site (IRES) sequence. The IRES sequence may be any viral, chromosomal or artificially designed sequence which initiates cap-independent ribosome binding to mRNA and facilitates the initiation of translation. Any solutes suitable for cell electroporation, which can contain factors facilitating cellular permeability and viability such as sugars, peptides, lipids, proteins, antioxidants, and surfactants can be included.

RNA can be introduced into target cells using any of a number of different methods, for instance, commercially available methods which include, but are not limited to, electroporation (Amaxa Nucleofector-II (Amaxa Biosystems, Cologne, Germany)), (ECM 830 (BTX) (Harvard Instruments, Boston, Mass.) or the Gene Pulser II (BioRad, Denver, Colo.), Multiporator (Eppendorf, Hamburg Germany), cationic liposome mediated transfection using lipofection, polymer encapsulation, peptide mediated transfection, or biolistic particle delivery systems such as "gene guns" (see, for example, Nishikawa, et al. Hum Gene Ther., 12(8):861-70 (2001)).

#### Non-Viral Delivery Methods

In some embodiments, non-viral methods can be used to deliver a nucleic acid encoding a CAR described herein into a cell or tissue or a subject.

In some embodiments, the non-viral method includes the use of a transposon (also called a transposable element). In some embodiments, a transposon is a piece of DNA that can insert itself at a location in a genome, for example, a piece of DNA that is capable of self-replicating and inserting its copy into a genome, or a piece of DNA that can be spliced out of a longer nucleic acid and inserted into another place in a genome. For example, a transposon comprises a DNA sequence made up of inverted repeats flanking genes for transposition.

Exemplary methods of nucleic acid delivery using a transposon include a Sleeping Beauty transposon system (SBTS) and a piggyBac<sup>TM</sup> (PB) transposon system. See, for

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example, Aronovich et al. Hum. Mol. Genet. 20.R1(2011): R14-20; Singh et al. Cancer Res. 15(2008):2961-2971; Huang et al. Mol. Ther. 16(2008):580-589; Grabundzija et al. Mol. Ther. 18(2010):1200-1209; Kebriaei et al. Blood. 122.21(2013):166; Williams. Molecular Therapy 16.9 (2008):1515-16; Bell et al. Nat. Protoc. 2.12(2007):3153-65; and Ding et al. Cell. 122.3(2005):473-83, all of which are incorporated herein by reference.

The SBTS includes two components: 1) a transposon containing a transgene and 2) a source of transposase enzyme. The transposase can transpose the transposon from a carrier plasmid (or other donor DNA) to a target DNA, such as a host cell chromosome/genome. For example, the transposase binds to the carrier plasmid/donor DNA, cuts the transposon (including transgene(s)) out of the plasmid, and inserts it into the genome of the host cell. See, for example, Aronovich et al. supra.

Exemplary transposons include a pT2-based transposon. See, for example, Grabundzija et al. Nucleic Acids Res. 41.3(2013):1829-47; and Singh et al. Cancer Res. 68.8 (2008): 2961-2971, all of which are incorporated herein by reference. Exemplary transposases include a Tc1/mariner-type transposase, for example, the SB10 transposase or the SB11 transposase (a hyperactive transposase which can be expressed, for example, from a cytomegalovirus promoter). See, for example, Aronovich et al.; Kebriaei et al.; and Grabundzija et al., all of which are incorporated herein by reference.

Use of the SBTS permits efficient integration and expression of a transgene, for example, a nucleic acid encoding a CAR described herein. Provided herein are methods of generating a cell, for example, T cell or NK cell, that stably expresses a CAR described herein, for example, using a transposon system such as SBTS.

In accordance with methods described herein, in some embodiments, one or more nucleic acids, for example, plasmids, containing the SBTS components are delivered to a cell (for example, T or NK cell). For example, the nucleic acid(s) are delivered by standard methods of nucleic acid (for example, plasmid DNA) delivery, for example, methods described herein, for example, electroporation, transfection, or lipofection. In some embodiments, the nucleic acid contains a transposon comprising a transgene, for example, a nucleic acid encoding a CAR described herein. In some embodiments, the nucleic acid contains a transposon comprising a transgene (for example, a nucleic acid encoding a CAR described herein) as well as a nucleic acid sequence encoding a transposase enzyme. In other embodiments, a system with two nucleic acids is provided, for example, a dual-plasmid system, for example, where a first plasmid contains a transposon comprising a transgene, and a second plasmid contains a nucleic acid sequence encoding a transposase enzyme. For example, the first and the second nucleic acids are co-delivered into a host cell.

In some embodiments, cells, for example, T or NK cells, are generated that express a CAR described herein by using a combination of gene insertion using the SBTS and genetic editing using a nuclease (for example, Zinc finger nucleases (ZFNs), Transcription Activator-Like Effector Nucleases (TALENs), the CRISPR/Cas system, or engineered meganuclease re-engineered homing endonucleases).

In some embodiments, use of a non-viral method of delivery permits reprogramming of cells, for example, T or NK cells, and direct infusion of the cells into a subject. Advantages of non-viral vectors include but are not limited to the ease and relatively low cost of producing sufficient

amounts required to meet a patient population, stability during storage, and lack of immunogenicity.

#### Methods of Manufacture/Production

The present invention also provides methods of making a cell disclosed herein, e.g., methods of engineering a T cell or NK cell to express a nucleic acid molecule encoding one or more CAR constructs described herein. In some embodiments, the manufacturing methods disclosed herein are used to manufacture a cell comprising a nucleic acid molecule encoding two CARs disclosed herein (e.g., an anti-BCMA CAR and an anti-CD19 CAR disclosed herein). In some embodiments, the manufacturing methods disclosed herein are used to manufacture a cell comprising a nucleic acid molecule encoding a diabody CAR disclosed herein, e.g., an anti-BCMA/anti-CD19 diabody CAR disclosed herein. In some embodiments, the manufacturing methods disclosed herein are used to manufacture a cell comprising two nucleic acid molecules, each of which encodes a CAR disclosed herein (e.g., one nucleic acid molecule encoding an anti-BCMA CAR and one nucleic acid molecule encoding an anti-CD19 CAR). In some embodiments, provided herein is a population of cells (for example, immune effector cells, for example, T cells or NK cells) made by any of the manufacturing processes described herein.

#### Activation Process

In some embodiments, the methods disclosed herein may manufacture immune effector cells engineered to express one or more CARs in less than 24 hours. Without wishing to be bound by theory, the methods provided herein preserve the undifferentiated phenotype of T cells, such as naïve T cells, during the manufacturing process. These CAR-expressing cells with an undifferentiated phenotype may persist longer and/or expand better *in vivo* after infusion. In some embodiments, CART cells produced by the manufacturing methods provided herein comprise a higher percentage of stem cell memory T cells, compared to CART cells produced by the traditional manufacturing process, e.g., as measured using scRNA-seq (e.g., as measured using methods described in Example 7 with respect to FIG. 25A). In some embodiments, CART cells produced by the manufacturing methods provided herein comprise a higher percentage of effector T cells, compared to CART cells produced by the traditional manufacturing process, e.g., as measured using scRNA-seq (e.g., as measured using methods described in Example 7 with respect to FIG. 25B). In some embodiments, CART cells produced by the manufacturing methods provided herein better preserve the stemness of T cells, compared to CART cells produced by the traditional manufacturing process, e.g., as measured using scRNA-seq (e.g., as measured using methods described in Example 7 with respect to FIG. 25C). In some embodiments, CART cells produced by the manufacturing methods provided herein show a lower level of hypoxia, compared to CART cells produced by the traditional manufacturing process, e.g., as measured using scRNA-seq (e.g., as measured using methods described in Example 7 with respect to FIG. 25D). In some embodiments, CART cells produced by the manufacturing methods provided herein show a lower level of autophagy, compared to CART cells produced by the traditional manufacturing process, e.g., as measured using scRNA-seq (e.g., as measured using methods described in Example 7 with respect to FIG. 25E). In some embodiments, the immune effector cells are engineered to comprise a nucleic acid molecule encoding two CARs disclosed herein (e.g., an anti-BCMA CAR and an anti-CD19 CAR disclosed herein). In some embodiments, the immune effector cells are engineered to comprise a nucleic acid molecule encoding a

diabody CAR disclosed herein, e.g., an anti-BCMA/anti-CD19 diabody CAR disclosed herein. In some embodiments, the immune effector cells are engineered to comprise two nucleic acid molecules, each of which encodes a CAR disclosed herein (e.g., one nucleic acid molecule encoding an anti-BCMA CAR and one nucleic acid molecule encoding an anti-CD19 CAR).

In some embodiments, the methods disclosed herein do not involve using a bead, such as Dynabeads® (for example, CD3/CD28 Dynabeads®), and do not involve a de-beading step. In some embodiments, the CART cells manufactured by the methods disclosed herein may be administered to a subject with minimal ex vivo expansion, for example, less than 1 day, less than 12 hours, less than 8 hours, less than 6 hours, less than 4 hours, less than 3 hours, less than 2 hours, less than 1 hour, or no ex vivo expansion. Accordingly, the methods described herein provide a fast manufacturing process of making improved CAR-expressing cell products for use in treating a disease in a subject.

In some embodiments, the present disclosure provides methods of making a population of cells (for example, T cells) that express a chimeric antigen receptor (CAR) (e.g., one or more CARs, e.g., two CARs) comprising: (i) contacting a population of cells (for example, T cells, for example, T cells isolated from a frozen or fresh leukapheresis product) with an agent that stimulates a CD3/TCR complex and/or an agent that stimulates a costimulatory molecule on the surface of the cells; (ii) contacting the population of cells (for example, T cells) with a nucleic acid molecule(s) (for example, a DNA or RNA molecule) encoding the CAR(s), thereby providing a population of cells (for example, T cells) comprising the nucleic acid molecule, and (iii) harvesting the population of cells (for example, T cells) for storage (for example, reformulating the population of cells in cryopreservation media) or administration, wherein: (a) step (ii) is performed together with step (i) or no later than 20 hours after the beginning of step (i), for example, no later than 12, 13, 14, 15, 16, 17, or 18 hours after the beginning of step (i), for example, no later than 18 hours after the beginning of step (i), and step (iii) is performed no later than 26 hours after the beginning of step (i), for example, no later than 22, 23, or 24 hours after the beginning of step (i), for example, no later than 24 hours after the beginning of step (i); (b) step (ii) is performed together with step (i) or no later than 20 hours after the beginning of step (i), for example, no later than 12, 13, 14, 15, 16, 17, or 18 hours after the beginning of step (i), for example, no later than 18 hours after the beginning of step (i), and step (iii) is performed no later than 30 hours after the beginning of step (ii), for example, no later than 22, 23, 24, 25, 26, 27, 28, 29, or 30 hours after the beginning of step (ii); or (c) the population of cells from step (iii) are not expanded, or expanded by no more than 5, 10, 15, 20, 25, 30, 35, or 40%, for example, no more than 10%, for example, as assessed by the number of living cells, compared to the population of cells at the beginning of step (i). In some embodiments, the nucleic acid molecule in step (ii) is a DNA molecule. In some embodiments, the nucleic acid molecule in step (ii) is an RNA molecule. In some embodiments, the nucleic acid molecule in step (ii) is on a viral vector, for example, a viral vector chosen from a lentivirus vector, an adenoviral vector, or a retrovirus vector. In some embodiments, the nucleic acid molecule in step (ii) is on a non-viral vector. In some embodiments, the nucleic acid molecule in step (ii) is on a plasmid. In some embodiments, the nucleic acid molecule in step (ii) is not on any vector. In some embodiments, step (ii)

comprises transducing the population of cells (for example, T cells) a viral vector(s) comprising a nucleic acid molecule encoding the CAR(s).

In some embodiments, the population of cells (for example, T cells) is collected from an apheresis sample (for example, a leukapheresis sample) from a subject.

In some embodiments, the apheresis sample (for example, a leukapheresis sample) is collected from the subject and shipped as a frozen sample (for example, a cryopreserved sample) to a cell manufacturing facility. Then the frozen apheresis sample is thawed, and T cells (for example, CD4+ T cells and/or CD8+ T cells) are selected from the apheresis sample, for example, using a cell sorting machine (for example, a ClinIMACS® Prodigy® device). The selected T cells (for example, CD4+ T cells and/or CD8+ T cells) are then seeded for CART manufacturing using the activation process described herein. In some embodiments, the selected T cells (for example, CD4+ T cells and/or CD8+ T cells) undergo one or more rounds of freeze-thaw before being seeded for CART manufacturing.

In some embodiments, the apheresis sample (for example, a leukapheresis sample) is collected from the subject and shipped as a fresh product (for example, a product that is not frozen) to a cell manufacturing facility. T cells (for example, CD4+ T cells and/or CD8+ T cells) are selected from the apheresis sample, for example, using a cell sorting machine (for example, a ClinIMACS® Prodigy® device). The selected T cells (for example, CD4+ T cells and/or CD8+ T cells) are then seeded for CART manufacturing using the activation process described herein. In some embodiments, the selected T cells (for example, CD4+ T cells and/or CD8+ T cells) undergo one or more rounds of freeze-thaw before being seeded for CART manufacturing.

In some embodiments, the apheresis sample (for example, a leukapheresis sample) is collected from the subject. T cells (for example, CD4+ T cells and/or CD8+ T cells) are selected from the apheresis sample, for example, using a cell sorting machine (for example, a ClinIMACS® Prodigy® device). The selected T cells (for example, CD4+ T cells and/or CD8+ T cells) are then shipped as a frozen sample (for example, a cryopreserved sample) to a cell manufacturing facility. The selected T cells (for example, CD4+ T cells and/or CD8+ T cells) are later thawed and seeded for CART manufacturing using the activation process described herein.

In some embodiments, cells (for example, T cells) are contacted with anti-CD3 and anti-CD28 antibodies for, for example, 12 hours, followed by transduction with a vector (for example, a lentiviral vector) (e.g. one or more vectors) encoding a CAR (e.g. one or more CARs). 24 hours after culture initiation, the cells are washed and formulated for storage or administration.

Without wishing to be bound by theory, brief CD3 and CD28 stimulation may promote efficient transduction of self-renewing T cells. Compared to traditional CART manufacturing approaches, the activation process provided herein does not involve prolonged ex vivo expansion. Similar to the cytokine process, the activation process provided herein also preserves undifferentiated T cells during CART manufacturing.

In some embodiments, the population of cells is contacted with an agent that stimulates a CD3/TCR complex and/or an agent that stimulates a costimulatory molecule on the surface of the cells.

In some embodiments, the agent that stimulates a CD3/TCR complex is an agent that stimulates CD3. In some embodiments, the agent that stimulates a costimulatory

molecule is an agent that stimulates CD28, ICOS, CD27, HVEM, LIGHT, CD40, 4-1BB, OX40, DR3, GITR, CD30, TIM1, CD2, CD226, or any combination thereof. In some embodiments, the agent that stimulates a costimulatory molecule is an agent that stimulates CD28. In some embodiments, the agent that stimulates a CD3/TCR complex is chosen from an antibody (for example, a single-domain antibody (for example, a heavy chain variable domain antibody), a peptibody, a Fab fragment, or a scFv), a small molecule, or a ligand (for example, a naturally-existing, recombinant, or chimeric ligand). In some embodiments, the agent that stimulates a CD3/TCR complex is an antibody. In some embodiments, the agent that stimulates a CD3/TCR complex is an anti-CD3 antibody. In some embodiments, the agent that stimulates a costimulatory molecule is chosen from an antibody (for example, a single-domain antibody (for example, a heavy chain variable domain antibody), a peptibody, a Fab fragment, or a scFv), a small molecule, or a ligand (for example, a naturally-existing, recombinant, or chimeric ligand). In some embodiments, the agent that stimulates a costimulatory molecule is an antibody. In some embodiments, the agent that stimulates a costimulatory molecule is an anti-CD28 antibody. In some embodiments, the agent that stimulates a CD3/TCR complex or the agent that stimulates a costimulatory molecule does not comprise a bead. In some embodiments, the agent that stimulates a CD3/TCR complex comprises an anti-CD3 antibody covalently attached to a colloidal polymeric nanomatrix. In some embodiments, the agent that stimulates a costimulatory molecule comprises an anti-CD28 antibody covalently attached to a colloidal polymeric nanomatrix. In some embodiments, the agent that stimulates a CD3/TCR complex and the agent that stimulates a costimulatory molecule comprise T Cell TransAct™.

In some embodiments, the matrix comprises or consists of a polymeric, for example, biodegradable or biocompatible inert material, for example, which is non-toxic to cells. In some embodiments, the matrix is composed of hydrophilic polymer chains, which obtain maximal mobility in aqueous solution due to hydration of the chains. In some embodiments, the mobile matrix may be of collagen, purified proteins, purified peptides, polysaccharides, glycosaminoglycans, or extracellular matrix compositions. A polysaccharide may include for example, cellulose ethers, starch, gum arabic, agarose, dextran, chitosan, hyaluronic acid, pectins, xanthan, guar gum or alginate. Other polymers may include polyesters, polyethers, polyacrylates, polyacrylamides, polyamines, polyethylene imines, polyquaternium polymers, polyphosphazenes, polyvinylalcohols, polyvinylacetates, polyvinylpyrrolidones, block copolymers, or polyurethanes. In some embodiments, the mobile matrix is a polymer of dextran.

In some embodiments, the population of cells is contacted with a nucleic acid molecule (e.g. one or more nucleic acid molecules) encoding a CAR (e.g. one or more CARs). In some embodiments, the population of cells is transduced with a DNA molecule (e.g. one or more DNA molecules) encoding a CAR (e.g. one or more CARs).

In some embodiments, in the case of a co-transduction of two nucleic acid molecules (e.g., lentiviral vectors), each of which encodes a CAR disclosed herein (e.g., one nucleic acid molecule encoding an anti-BCMA CAR and one nucleic acid molecule encoding an anti-CD19 CAR, as disclosed herein), each of the vectors containing nucleic acid molecules encoding the CAR can be added to the reaction mixture (e.g., containing a cell population) at a different multiplicity of infection (MOI).

Without wishing to be bound by theory, it is believed that, in some embodiments, using different MOIs for the vectors containing nucleic acid molecules which encode distinct CAR molecules may affect the final composition of the cellular population. For example, in the case of a co-transduction of a lentiviral vector encoding an anti-BCMA CAR and a lentiviral vector encoding an anti-CD19 CAR, different MOIs can be used to maximize the percent of mono BCMA CART cells and BCMA/CD19 dual CART cells, while resulting in fewer mono CD19 CART cells and untransduced cells.

In some embodiments, in the case of a co-transduction of a lentiviral vector encoding an anti-BCMA CAR and a lentiviral vector encoding an anti-CD19 CAR, a population of cells is contacted with the first viral vector at a multiplicity of infection (MOI) that is higher than, equal to, or less than an MOI at which the population of cells is contacted with the second viral vector. In some embodiments, the population of cells is contacted with the first viral vector at a multiplicity of infection (MOI) that is higher than an MOI at which the population of cells is contacted with the second viral vector.

In some embodiments, the population of cells is contacted with the first viral vector at a first MOI and with the second viral vector at a second MOI, such that a resultant population of cells comprises a first population of cells that comprise the anti-BCMA CAR but not the anti-CD19 CAR, a second population of cells that comprise the anti-CD19 CAR but not the anti-BCMA CAR, and a third population of cells that comprise both the anti-BCMA CAR and the anti-CD19 CAR, wherein:

- (a) the total number of viable cells in the second and third populations combined is less than or equal to about 110% (e.g., less than or equal to about 105%, 100%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, 5%, 1%, or less) of the total number of viable cells in the first and third populations combined, e.g., as determined by a method described in Example 10;
- (b) the total number of viable cells in the first and third populations combined is greater than or equal to about 90% (e.g., greater than or equal to about 100%, 125%, 150%, 175%, 200%, 250%, 300%, 400%, 500%, 750%, 1000%, 2000%, 5000, 10000% or more) of the total number of viable cells in the second and third populations combined, e.g., as determined by a method described in Example 10;
- (c) the total number of viable cells in the first and third populations combined is greater than or equal to about 5% (e.g., greater than or equal to about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90%) of the total number of viable cells in the resultant population, e.g., as determined by a method described in Example 10;
- (d) the total number of viable cells in the second population is less than or equal to about 110% (e.g., less than or equal to about 105%, 100%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, 5%, 1%, or less) of the total number of viable cells in the first and third populations combined, e.g., as determined by a method described in Example 10; or
- (e) the total number of viable cells in the first and third populations combined is greater than or equal to about 90% (e.g., greater than or equal to about 100%, 125%, 150%, 175%, 200%, 250%, 300%, 400%, 500%, 750%, 1000%, 2000%, 5000, 10000% or more) of the total number of viable cells in the second population, e.g., as determined by a method described in Example 10;

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In some embodiments, the population of cells is contacted with the second viral vector at an MOI (e.g., an MOI that is sufficiently lower than an MOI at which the population of cells is contacted with the first viral vector, such that in a resultant population of cells:

- (a) the total number of viable cells in the second and third populations combined is less than or equal to about 110% (e.g., less than or equal to about 105%, 100%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, 5%, 1%, or less) of the total number of viable cells in the first and third populations combined, e.g., as determined by a method described in Example 10;
- (b) the total number of viable cells in the first and third populations combined is greater than or equal to about 90% (e.g., greater than or equal to about 100%, 125%, 150%, 175%, 200%, 250%, 300%, 400%, 500%, 750%, 1000%, 2000%, 5000, 10000% or more) of the total number of viable cells in the second and third populations combined, e.g., as determined by a method described in Example 10;
- (c) the total number of viable cells in the first and third populations combined is greater than or equal to about 5% (e.g., greater than or equal to about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90%) of the total number of viable cells in the resultant population, e.g., as determined by a method described in Example 10;
- (d) the total number of viable cells in the second population is less than or equal to about 110% (e.g., less than or equal to about 105%, 100%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, 5%, 1%, or less) of the total number of viable cells in the first and third populations combined, e.g., as determined by a method described in Example 10; or
- (e) the total number of viable cells in the first and third populations combined is greater than or equal to about 90% (e.g., greater than or equal to about 100%, 125%, 150%, 175%, 200%, 250%, 300%, 400%, 500%, 750%, 1000%, 2000%, 5000, 10000% or more) of the total number of viable cells in the second population, e.g., as determined by a method described in Example 10.

In some embodiments, the population of cells is contacted with the first viral vector at a first MOI, and the population of cells is contacted with the second viral vector at a second MOI, such that a resultant population of cells comprises:

- (a) the total number of viable cells in the second and third populations combined is less than or equal to about 110% (e.g., less than or equal to about 105%, 100%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, 5%, 1%, or less) of the total number of viable cells in the first and third populations combined, e.g., as determined by a method described in Example 10;
- (b) the total number of viable cells in the first and third populations combined is greater than or equal to about 90% (e.g., greater than or equal to about 100%, 125%, 150%, 175%, 200%, 250%, 300%, 400%, 500%, 750%, 1000%, 2000%, 5000, 10000% or more) of the total number of viable cells in the second and third populations combined, e.g., as determined by a method described in Example 10;
- (c) the total number of viable cells in the first and third populations combined is greater than or equal to about 5% (e.g., greater than or equal to about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90%) of the total number of viable cells in the resultant population, e.g., as determined by a method described in Example 10;

- (d) the total number of viable cells in the second population is less than or equal to about 110% (e.g., less than or equal to about 105%, 100%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, 5%, 1%, or less) of the total number of viable cells in the first and third populations combined, e.g., as determined by a method described in Example 10; or
- (e) the total number of viable cells in the first and third populations combined is greater than or equal to about 90% (e.g., greater than or equal to about 100%, 125%, 150%, 175%, 200%, 250%, 300%, 400%, 500%, 750%, 1000%, 2000%, 5000, 10000% or more) of the total number of viable cells in the second population, e.g., as determined by a method described in Example 10.

In some embodiments, the population of cells is contacted with:

- (a) the first viral vector at an MOI of about 1 to about 10 (e.g., about 2 to about 9, about 3 to about 8, about 4 to about 7, about 5 to about 6, about 1 to about 8, about 1 to about 6, about 1 to about 4, about 8 to about 10, about 6 to about 10, about 4 to about 10, about 1 to about 3, about 2 to about 4, about 3 to about 5, about 4 to about 6, about 5 to about 7, about 6 to about 8, about 7 to about 9, about 8 to about 10, about 2.5 to about 5, about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, or about 10);
- (b) the second viral vector at an MOI of about 0.1 to about 5 (e.g., about 0.2 to about 4, about 0.3 to about 3, about 0.4 to about 2, about 0.5 to about 1, about 0.6 to about 0.9, about 0.7 to about 0.8, about 0.1 to about 4, about 0.1 to about 3, about 0.1 to about 2, about 0.1 to about 1, about 0.1 to about 0.5, about 4 to about 5, about 3 to about 5, about 2 to about 5, about 1 to about 5, about 0.5 to about 5, about 0.2 to about 5, about 0.1 to about 0.5, about 0.2 to about 1, about 0.5 to about 2, about 1 to about 3, about 2 to about 4, about 3 to about 5, about 0.5 to about 1, about 0.1, about 0.2, about 0.3, about 0.4, about 0.5, about 0.6, about 0.7, about 0.8, about 0.9, about 1, about 2, about 3, about 4, or about 5);
- (c) the first viral vector at an MOI that is at least about 10% (e.g., at least about 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90%) or at least about 1 fold (e.g., at least about 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, or 100 fold, e.g., about 2 to about 50 fold, about 3 to 20 fold, about 5 to about 15 fold, or about 8 to about 10 fold) higher than an MOI at which the population of cells is contacted with the second viral vector; and/or
- (d) the second viral vector at an MOI that is no more than 1/X, wherein X is 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 20, 30, 40, 50, 60, 70, 80, 90, or 100, of an MOI at which the population of cells is contacted with the first viral vector.

In some embodiments, the population of cells is contacted with the first viral vector at an MOI of about 2.5 to about 5. In some embodiments, the population of cells is contacted with the second viral vector at an MOI of about 0.5 to about 1.0. In some embodiments, the first viral vector at an MOI that is about 8 to about 10 fold higher than an MOI at which the population of cells is contacted with the second viral vector. In some embodiments, the second viral vector at an MOI that is no more than 1/X, wherein X is 6, 8, 10, or 12, of an MOI at which the population of cells is contacted with the first viral vector.

In some embodiments, in step (ii), the population of cells is contacted with:

- (a) the first viral vector at an MOI of between about 4 and about 5 (e.g., about 4.75); and/or
  - (b) the second viral vector at an MOI between about 0.2 and about 1 (e.g., about 0.5).
- 5 In some embodiments, in step (ii), the population of cells comprises about  $1 \times 10^8$  to about  $5 \times 10^9$  (e.g., about  $2 \times 10^8$  to about  $2 \times 10^9$  or about  $4 \times 10^8$  to about  $1 \times 10^9$  total viable cells. In some embodiments, the cells are suspended in a culture at a concentration of about  $1 \times 10^6$  to about  $1 \times 10^7$  (e.g., about 10  $2 \times 10^6$  to about  $5 \times 10^6$  or about  $3 \times 10^6$  to about  $4 \times 10^6$ ) viable cells/mL.
- The precise MOI used for each vector can be adjusted or determined based on a number of factors, including, but not limited to, properties of the batch of viral vector, characteristics of the cells to be transduced, and transduction efficiency. In some embodiments, contacting the population of cells with the nucleic acid molecule(s) encoding the CAR(s) occurs simultaneously with contacting the population of cells with the agent that stimulates a CD3/TCR complex and/or the agent that stimulates a costimulatory molecule on the surface of the cells described above. In some embodiments, contacting the population of cells with the nucleic acid molecule(s) encoding the CAR(s) occurs no later than 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 20, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0.5 hours after the beginning of contacting the population of cells with the agent that stimulates a CD3/TCR complex and/or the agent that stimulates a costimulatory molecule on the surface of the cells described above. In some embodiments, contacting 25 the population of cells with the nucleic acid molecule(s) encoding the CAR(s) occurs no later than 20 hours after the beginning of contacting the population of cells with the agent that stimulates a CD3/TCR complex and/or the agent that stimulates a costimulatory molecule on the surface of the cells described above. In some embodiments, contacting 30 the population of cells with the nucleic acid molecule(s) encoding the CAR(s) occurs no later than 19 hours after the beginning of contacting the population of cells with the agent that stimulates a CD3/TCR complex and/or the agent that stimulates a costimulatory molecule on the surface of the cells described above. In some embodiments, contacting 35 the population of cells with the nucleic acid molecule(s) encoding the CAR(s) occurs no later than 18 hours after the beginning of contacting the population of cells with the agent that stimulates a CD3/TCR complex and/or the agent that stimulates a costimulatory molecule on the surface of the cells described above. In some embodiments, contacting 40 the population of cells with the nucleic acid molecule(s) encoding the CAR(s) occurs no later than 17 hours after the beginning of contacting the population of cells with the agent that stimulates a CD3/TCR complex and/or the agent that stimulates a costimulatory molecule on the surface of the cells described above. In some embodiments, contacting 45 the population of cells with the nucleic acid molecule(s) encoding the CAR(s) occurs no later than 16 hours after the beginning of contacting the population of cells with the agent that stimulates a CD3/TCR complex and/or the agent that stimulates a costimulatory molecule on the surface of the cells described above. In some embodiments, contacting 50 the population of cells with the nucleic acid molecule(s) encoding the CAR(s) occurs no later than 15 hours after the beginning of contacting the population of cells with the agent that stimulates a CD3/TCR complex and/or the agent that stimulates a costimulatory molecule on the surface of the cells described above. In some embodiments, contacting 55 the population of cells with the nucleic acid molecule(s) encoding the CAR(s) occurs no later than 14 hours after the beginning of contacting the population of cells with the agent that stimulates a CD3/TCR complex and/or the agent that stimulates a costimulatory molecule on the surface of the cells described above. In some embodiments, contacting 60 the population of cells with the nucleic acid molecule(s) encoding the CAR(s) occurs no later than 13 hours after the beginning of contacting the population of cells with the agent that stimulates a CD3/TCR complex and/or the agent that stimulates a costimulatory molecule on the surface of the cells described above. In some embodiments, contacting 65 the population of cells with the nucleic acid molecule(s) encoding the CAR(s) occurs no later than 12 hours after the beginning of contacting the population of cells with the agent that stimulates a CD3/TCR complex and/or the agent that stimulates a costimulatory molecule on the surface of the cells described above.

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agent that stimulates a CD3/TCR complex and/or the agent that stimulates a costimulatory molecule on the surface of the cells described above. In some embodiments, contacting the population of cells with the nucleic acid molecule(s) encoding the CAR(s) occurs no later than 3 hours after the beginning of contacting the population of cells with the agent that stimulates a CD3/TCR complex and/or the agent that stimulates a costimulatory molecule on the surface of the cells described above. In some embodiments, contacting the population of cells with the nucleic acid molecule(s) encoding the CAR(s) occurs no later than 2 hours after the beginning of contacting the population of cells with the agent that stimulates a CD3/TCR complex and/or the agent that stimulates a costimulatory molecule on the surface of the cells described above. In some embodiments, contacting the population of cells with the nucleic acid molecule(s) encoding the CAR(s) occurs no later than 1 hour after the beginning of contacting the population of cells with the agent that stimulates a CD3/TCR complex and/or the agent that stimulates a costimulatory molecule on the surface of the cells described above. In some embodiments, contacting the population of cells with the nucleic acid molecule(s) encoding the CAR(s) occurs no later than 30 minutes after the beginning of contacting the population of cells with the agent that stimulates a CD3/TCR complex and/or the agent that stimulates a costimulatory molecule on the surface of the cells described above.

In some embodiments, the population of cells is harvested for storage or administration.

In some embodiments, the population of cells is harvested for storage or administration no later than 72, 60, 48, 36, 32, 31, 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, or 18 hours after the beginning of contacting the population of cells with the agent that stimulates a CD3/TCR complex and/or the agent that stimulates a costimulatory molecule on the surface of the cells described above. In some embodiments, the population of cells is harvested for storage or administration no later than 26 hours after the beginning of contacting the population of cells with the agent that stimulates a CD3/TCR complex and/or the agent that stimulates a costimulatory molecule on the surface of the cells described above. In some embodiments, the population of cells is harvested for storage or administration no later than 25 hours after the beginning of contacting the population of cells with the agent that stimulates a CD3/TCR complex and/or the agent that stimulates a costimulatory molecule on the surface of the cells described above. In some embodiments, the population of cells is harvested for storage or administration no later than 24 hours after the beginning of contacting the population of cells with the agent that stimulates a CD3/TCR complex and/or the agent that stimulates a costimulatory molecule on the surface of the cells described above. In some embodiments, the population of cells is harvested for storage or administration no later than 23 hours after the beginning of contacting the population of cells with the agent that stimulates a CD3/TCR complex and/or the agent that stimulates a costimulatory molecule on the surface of the cells described above. In some embodiments, the population of cells is harvested for storage or administration no later than 22 hours after the beginning of contacting the population of cells with the agent that stimulates a CD3/TCR complex and/or the agent that stimulates a costimulatory molecule on the surface of the cells described above.

In some embodiments, the population of cells is not expanded ex vivo.

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18, 19, 20, 25, 30, 35, 40, 45, 50, 55, or 60%, for example, as assessed by the number of living cells, compared to the population of cells before it is contacted with the agent that stimulates a CD3/TCR complex and/or the agent that stimulates a costimulatory molecule on the surface of the cells described above. In some embodiments, the population of cells is expanded by no more than 5%, for example, as assessed by the number of living cells, compared to the population of cells before it is contacted with the agent that stimulates a CD3/TCR complex and/or the agent that stimulates a costimulatory molecule on the surface of the cells described above. In some embodiments, the population of cells is expanded by no more than 10%, for example, as assessed by the number of living cells, compared to the population of cells before it is contacted with the agent that stimulates a CD3/TCR complex and/or the agent that stimulates a costimulatory molecule on the surface of the cells described above. In some embodiments, the population of cells is expanded by no more than 15%, for example, as assessed by the number of living cells, compared to the population of cells before it is contacted with the agent that stimulates a CD3/TCR complex and/or the agent that stimulates a costimulatory molecule on the surface of the cells described above. In some embodiments, the population of cells is expanded by no more than 20%, for example, as assessed by the number of living cells, compared to the population of cells before it is contacted with the agent that stimulates a CD3/TCR complex and/or the agent that stimulates a costimulatory molecule on the surface of the cells described above. In some embodiments, the population of cells is expanded by no more than 25%, for example, as assessed by the number of living cells, compared to the population of cells before it is contacted with the agent that stimulates a CD3/TCR complex and/or the agent that stimulates a costimulatory molecule on the surface of the cells described above. In some embodiments, the population of cells is expanded by no more than 30%, for example, as assessed by the number of living cells, compared to the population of cells before it is contacted with the agent that stimulates a CD3/TCR complex and/or the agent that stimulates a costimulatory molecule on the surface of the cells described above. In some embodiments, the population of cells is expanded by no more than 35%, for example, as assessed by the number of living cells, compared to the population of cells before it is contacted with the agent that stimulates a CD3/TCR complex and/or the agent that stimulates a costimulatory molecule on the surface of the cells described above. In some embodiments, the population of cells is expanded by no more than 40%, for example, as assessed by the number of living cells, compared to the population of cells before it is contacted with the agent that stimulates a CD3/TCR complex and/or the agent that stimulates a costimulatory molecule on the surface of the cells described above.

In some embodiments, the population of cells is expanded by no more than 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 9, 10, 11, 12, 16, 20, 24, 36, or 48 hours, for example, as assessed by the number of living cells, compared to the population of cells before it is contacted with the one or more cytokines described above.

In some embodiments, the activation process is conducted in serum free cell media. In some embodiments, the activation process is conducted in cell media comprising one or more cytokines chosen from: IL-2, IL-15 (for example, hetIL-15 (IL15/sIL-15Ra)), or IL-6 (for example, IL-6/sIL-6Ra). In some embodiments, hetIL-15 comprises the amino acid sequence of NWVNVISDLKKIEDLIQSM-

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HIDATLYTESDVHPSCKVTAMKCFLLELQVISLESG-DASIHDV  
EN LIILANNSSLSSNGNVTESGCKE-CEELEEKNIKEFLQSFVHIVQMFINTSITCPPMSVE-HADIWVK  
5 SYSLYSRERYICNSGFKRKAGTSSLTECVLNKATN-VAHWTTPLSKCIRDPAVLHQRPAPPSTVT  
TAGVTPQPESLSPSGKEPAASSPSSNNTAAT-TAAIIVPGSQLMPSKSPSTGTTEISSHESSHGTPSQ  
TAKNWELTASASHQPPGVYPQG (SEQ ID NO: 309). In  
10 some embodiments, hetIL-15 comprises an amino acid sequence having at least about 70, 75, 80, 85, 90, 95, or 99% identity to SEQ ID NO: 309. In some embodiments, the activation process is conducted in cell media comprising a LSD1 inhibitor. In some embodiments, the activation process is conducted in cell media comprising a MALT1 inhibitor. In some embodiments, the serum free cell media comprises a serum replacement. In some embodiments, the serum replacement is CT<sup>TM</sup> Immune Cell Serum Replacement (ICSR). In some embodiments, the level of ICSR can  
15 be, for example, up to 5%, for example, about 1%, 2%, 3%, 4%, or 5%. Without wishing to be bound by theory, using cell media, for example, Rapid Media shown in Table 21 or Table 25, comprising ICSR, for example, 2% ICSR, may improve cell viability during a manufacture process  
20 described herein.  
In some embodiments, the present disclosure provides methods of making a population of cells (for example, T cells) that express a chimeric antigen receptor (CAR) comprising: (a) providing an apheresis sample (for example, a fresh or cryopreserved leukapheresis sample) collected from a subject; (b) selecting T cells from the apheresis sample (for example, using negative selection, positive selection, or selection without beads); (c) seeding isolated T cells at, for example, 1×10<sup>6</sup> to 1×10<sup>7</sup> cells/mL; (d) contacting T cells  
25 with an agent that stimulates T cells, for example, an agent that stimulates a CD3/TCR complex and/or an agent that stimulates a costimulatory molecule on the surface of the cells (for example, contacting T cells with anti-CD3 and/or anti-CD28 antibody, for example, contacting T cells with TransAct); (e) contacting T cells with a nucleic acid molecule(s) (for example, a DNA or RNA molecule) encoding the CAR(s) (for example, contacting T cells with a virus comprising a nucleic acid molecule(s) encoding the CAR(s)) for, for example, 6-48 hours, for example, 20-28 hours; and  
30 (f) washing and harvesting T cells for storage (for example, reformulating T cells in cryopreservation media) or administration. In some embodiments, step (f) is performed no later than 30 hours after the beginning of step (d) or (e), for example, no later than 22, 23, 24, 25, 26, 27, 28, 29, or 30 hours after the beginning of step (d) or (e).

In some embodiments, provided herein is a population of cells (for example, immune effector cells, for example, T cells or NK cells) made by any of the manufacturing processes described herein (e.g., the Activation Process described herein).

In some embodiments, the percentage of naïve cells, for example, naïve T cells, for example, CD45RA+CD45RO-CCR7+ T cells, in the population of cells at the end of the manufacturing process (for example, at the end of the cytokine process or the activation process described herein) (1) is the same as, (2) differs, for example, by no more than 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15%, from, or (3) is increased, for example, by at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25%, as compared to, the percentage of naïve cells, for example, naïve T cells, for example, CD45RA+CD45RO- CCR7+ cells, in the population of cells at the beginning of the

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manufacturing process (for example, at the beginning of the cytokine process or the activation process described herein). In some embodiments, the population of cells at the end of the manufacturing process (for example, at the end of the cytokine process or the activation process described herein) shows a higher percentage of naïve cells, for example, naïve T cells, for example, CD45RA+CD45RO- CCR7+ T cells (for example, at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, or 50% higher), compared with cells made by an otherwise similar method which lasts, for example, more than 26 hours (for example, which lasts more than 5, 6, 7, 8, 9, 10, 11, or 12 days) or which involves expanding the population of cells in vitro for, for example, more than 3 days (for example, expanding the population of cells in vitro for 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 days).

In some embodiments, the percentage of naïve cells, for example, naïve T cells, for example, CD45RA+CD45RO- CCR7+ T cells, in the population of cells at the end of the manufacturing process (for example, at the end of the cytokine process or the activation process described herein) is not less than 20, 25, 30, 35, 40, 45, 50, 55, or 60%.

In some embodiments, the percentage of central memory cells, for example, central memory T cells, for example, CD95+ central memory T cells, in the population of cells at the end of the manufacturing process (for example, at the end of the cytokine process or the activation process described herein) (1) is the same as, (2) differs, for example, by no more than 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15% from, or (3) is decreased, for example, by at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25%, as compared to, the percentage of central memory cells, for example, central memory T cells, for example, CD95+ central memory T cells, in the population of cells at the beginning of the manufacturing process (for example, at the beginning of the cytokine process or the activation process described herein). In some embodiments, the population of cells at the end of the manufacturing process (for example, at the end of the cytokine process or the activation process described herein) shows a lower percentage of central memory cells, for example, central memory T cells, for example, CD95+ central memory T cells (for example, at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, or 50% lower), compared with cells made by an otherwise similar method which lasts, for example, more than 26 hours (for example, which lasts more than 5, 6, 7, 8, 9, 10, 11, or 12 days) or which involves expanding the population of cells in vitro for, for example, more than 3 days (for example, expanding the population of cells in vitro for 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 days).

In some embodiments, the percentage of central memory cells, for example, central memory T cells, for example, CD95+ central memory T cells, in the population of cells at the end of the manufacturing process (for example, at the end of the cytokine process or the activation process described herein) is no more than 40, 45, 50, 55, 60, 65, 70, 75, or 80%.

In some embodiments, the population of cells at the end of the manufacturing process (for example, at the end of the cytokine process or the activation process described herein) after being administered *in vivo*, persists longer or expands at a higher level (for example, at least 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, or 90% higher), compared with cells made by an otherwise similar method which lasts, for example, more than 26 hours (for example, which lasts more than 5, 6, 7, 8, 9, 10, 11, or 12 days) or which involves expanding the population of cells in vitro for, for example,

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more than 3 days (for example, expanding the population of cells *in vitro* for 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 days).

In some embodiments, the population of cells has been enriched for IL6R-expressing cells (for example, cells that are positive for IL6R $\alpha$  and/or IL6R $\beta$ ) prior to the beginning of the manufacturing process (for example, prior to the beginning of the cytokine process or the activation process described herein). In some embodiments, the population of cells comprises, for example, no less than 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, or 80% of IL6R-expressing cells (for example, cells that are positive for IL6R $\alpha$  and/or IL6R $\beta$ ) at the beginning of the manufacturing process (for example, at the beginning of the cytokine process or the activation process described herein).

#### Cytokine Process

In some embodiments, the present disclosure provides methods of making a population of cells (for example, T cells) that express a chimeric antigen receptor (CAR) (e.g., one or more CARs, e.g., two CARs) comprising: (1) contacting a population of cells with a cytokine chosen from IL-2, IL-7, IL-15, IL-21, IL-6, or a combination thereof, (2) contacting the population of cells (for example, T cells) with a nucleic acid molecule(s) (for example, a DNA or RNA molecule) encoding the CAR(s), thereby providing a population of cells (for example, T cells) comprising the nucleic acid molecule, and (3) harvesting the population of cells (for example, T cells) for storage (for example, reformulating the population of cells in cryopreservation media) or administration, wherein: (a) step (2) is performed together with step (1) or no later than 5 hours after the beginning of step (1), for example, no later than 1, 2, 3, 4, or 5 hours after the beginning of step (1), and step (3) is performed no later than 26 hours after the beginning of step (1), for example, no later than 22, 23, or 24 hours after the beginning of step (1), for example, no later than 24 hours after the beginning of step (1), or (b) the population of cells from step (3) are not expanded, or expanded by no more than 5, 10, 15, 20, 25, 30, 35, or 40%, for example, no more than 10%, for example, as assessed by the number of living cells, compared to the population of cells at the beginning of step (1). In some embodiments, the nucleic acid molecule in step (2) is a DNA molecule. In some embodiments, the nucleic acid molecule in step (2) is an RNA molecule. In some embodiments, the nucleic acid molecule in step (2) is on a viral vector, for example, a viral vector chosen from a lentivirus vector, an adenoviral vector, or a retrovirus vector. In some embodiments, the nucleic acid molecule in step (2) is on a non-viral vector. In some embodiments, the nucleic acid molecule in step (2) is on a plasmid. In some embodiments, the nucleic acid molecule in step (2) is not on any vector. In some embodiments, step (2) comprises transducing the population of cells (for example, T cells) with a viral vector comprising a nucleic acid molecule(s) encoding the CAR(s). In some embodiments, the cells are engineered to comprise a nucleic acid molecule encoding two CARs disclosed herein (e.g., an anti-BCMA CAR and an anti-CD19 CAR disclosed herein). In some embodiments, the cells are engineered to comprise a nucleic acid molecule encoding a diabody CAR disclosed herein, e.g., an anti-BCMA/anti-CD19 diabody CAR disclosed herein. In some embodiments, the cells are engineered to comprise two nucleic acid molecules, each of which encodes a CAR disclosed herein (e.g., one nucleic acid molecule encoding an anti-BCMA CAR and one nucleic acid molecule encoding an anti-CD19 CAR).

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In some embodiments, the population of cells (for example, T cells) is collected from an apheresis sample (for example, a leukapheresis sample) from a subject.

In some embodiments, the apheresis sample (for example, a leukapheresis sample) is collected from the subject and shipped as a frozen sample (for example, a cryopreserved sample) to a cell manufacturing facility. The frozen apheresis sample is then thawed, and T cells (for example, CD4+ T cells and/or CD8+ T cells) are selected from the apheresis sample, for example, using a cell sorting machine (for example, a ClinIMACS® Prodigy® device). The selected T cells (for example, CD4+ T cells and/or CD8+ T cells) are then seeded for CART manufacturing using the cytokine process described herein. In some embodiments, at the end of the cytokine process, the CAR T cells are cryopreserved and later thawed and administered to the subject. In some embodiments, the selected T cells (for example, CD4+ T cells and/or CD8+ T cells) undergo one or more rounds of freeze-thaw before being seeded for CART manufacturing.

In some embodiments, the apheresis sample (for example, a leukapheresis sample) is collected from the subject and shipped as a fresh product (for example, a product that is not frozen) to a cell manufacturing facility. T cells (for example, CD4+ T cells and/or CD8+ T cells) are selected from the apheresis sample, for example, using a cell sorting machine (for example, a ClinIMACS® Prodigy® device). The selected T cells (for example, CD4+ T cells and/or CD8+ T cells) are then seeded for CART manufacturing using the cytokine process described herein. In some embodiments, the selected T cells (for example, CD4+ T cells and/or CD8+ T cells) undergo one or more rounds of freeze-thaw before being seeded for CART manufacturing.

In some embodiments, the apheresis sample (for example, a leukapheresis sample) is collected from the subject. T cells (for example, CD4+ T cells and/or CD8+ T cells) are selected from the apheresis sample, for example, using a cell sorting machine (for example, a ClinIMACS® Prodigy® device). The selected T cells (for example, CD4+ T cells and/or CD8+ T cells) are then shipped as a frozen sample (for example, a cryopreserved sample) to a cell manufacturing facility. The selected T cells (for example, CD4+ T cells and/or CD8+ T cells) are later thawed and seeded for CART manufacturing using the cytokine process described herein.

In some embodiments, after cells (for example, T cells) are seeded, one or more cytokines (for example, one or more cytokines chosen from IL-2, IL-7, IL-15 (for example, hetIL-15 (IL15/sIL-15Ra)), IL-21, or IL-6 (for example, IL-6/sIL-6R)) as well as a vector (for example, a lentiviral vector) (e.g. one or more vectors) encoding a CAR (e.g., one or more CARs) are added to the cells. After incubation for 20-24 hours, the cells are washed and formulated for storage or administration.

Different from traditional CART manufacturing approaches, the cytokine process provided herein does not involve CD3 and/or CD28 stimulation, or ex vivo T cell expansion. T cells that are contacted with anti-CD3 and anti-CD28 antibodies and expanded extensively ex vivo tend to show differentiation towards a central memory phenotype. Without wishing to be bound by theory, the cytokine process provided herein preserves or increases the undifferentiated phenotype of T cells during CART manufacturing, generating a CART product that may persist longer after being infused into a subject.

In some embodiments, the population of cells is contacted with one or more cytokines (for example, one or more

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cytokines chosen from IL-2, IL-7, IL-15 (for example, hetIL-15 (IL15/sIL-15Ra)), IL-21, or IL-6 (for example, IL-6/sIL-6Ra).

In some embodiments, the population of cells is contacted with IL-2. In some embodiments, the population of cells is contacted with IL-7. In some embodiments, the population of cells is contacted with IL-15 (for example, hetIL-15 (IL15/sIL-15Ra)). In some embodiments, the population of cells is contacted with IL-21. In some embodiments, the population of cells is contacted with IL-6 (for example, IL-6/sIL-6Ra). In some embodiments, the population of cells is contacted with IL-2 and IL-7. In some embodiments, the population of cells is contacted with IL-2 and IL-15 (for example, hetIL-15 (IL15/sIL-15Ra)). In some embodiments, the population of cells is contacted with IL-2 and IL-21. In some embodiments, the population of cells is contacted with IL-2 and IL-6 (for example, IL-6/sIL-6Ra). In some embodiments, the population of cells is contacted with IL-7 and IL-15 (for example, hetIL-15 (IL15/sIL-15Ra)). In some embodiments, the population of cells is contacted with IL-7 and IL-21. In some embodiments, the population of cells is contacted with IL-2 and IL-21. In some embodiments, the population of cells is contacted with IL-2 and IL-6 (for example, IL-6/sIL-6Ra). In some embodiments, the population of cells is contacted with IL-7 and IL-15 (for example, hetIL-15 (IL15/sIL-15Ra)). In some embodiments, the population of cells is contacted with IL-7 and IL-21. In some embodiments, the population of cells is contacted with IL-7 and IL-6 (for example, IL-6/sIL-6Ra). In some embodiments, the population of cells is contacted with IL-15 (for example, hetIL-15 (IL15/sIL-15Ra)) and IL-21. In some embodiments, the population of cells is contacted with IL-15 (for example, hetIL-15 (IL15/sIL-15Ra)) and IL-6 (for example, IL-6/sIL-6Ra). In some embodiments, the population of cells is contacted with IL-21 and IL-6 (for example, IL-6/sIL-6Ra). In some embodiments, the population of cells is contacted with IL-7, IL-15 (for example, hetIL-15 (IL15/sIL-15Ra)), and IL-21. In some embodiments, the population of cells is further contacted with a LSD1 inhibitor. In some embodiments, the population of cells is further contacted with a MALT1 inhibitor.

In some embodiments, the population of cells is contacted with 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, or 300 U/ml of IL-2. In some embodiments, the population of cells is contacted with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 ng/ml of IL-7. In some embodiments, the population of cells is contacted with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 ng/ml of IL-15.

In some embodiments, the population of cells is contacted with a nucleic acid molecule (e.g. one or more nucleic acid molecules) encoding a CAR (e.g., one or more CARs). In some embodiments, the population of cells is transduced with a DNA molecule (e.g. one or more DNA molecules) encoding a CAR (e.g. one or more CARs).

In some embodiments, contacting the population of cells with the nucleic acid molecule encoding the CAR(s) occurs simultaneously with contacting the population of cells with the one or more cytokines described above. In some embodiments, contacting the population of cells with the nucleic acid molecule encoding the CAR(s) occurs no later than 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5 or 10 hours after the beginning of contacting the population of cells with the one or more cytokines described above. In some embodiments, contacting the population of cells with the nucleic acid molecule encoding the CAR(s) occurs no later than 5 hours after the beginning of contacting the population of cells with the one or more cytokines described above. In some embodiments, contacting the population of cells with the nucleic acid molecule encoding the CAR(s) occurs no later than 4 hours after the beginning of contacting the population of cells with the one or more cytokines

described above. In some embodiments, contacting the population of cells with the nucleic acid molecule encoding the CAR(s) occurs no later than 3 hours after the beginning of contacting the population of cells with the one or more cytokines described above. In some embodiments, contacting the population of cells with the nucleic acid molecule encoding the CAR(s) occurs no later than 2 hours after the beginning of contacting the population of cells with the one or more cytokines described above. In some embodiments, contacting the population of cells with the nucleic acid molecule encoding the CAR(s) occurs no later than 1 hour after the beginning of contacting the population of cells with the one or more cytokines described above.

In some embodiments, the population of cells is harvested for storage or administration.

In some embodiments, the population of cells is harvested for storage or administration no later than 72, 60, 48, 36, 32, 31, 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, or 18 hours after the beginning of contacting the population of cells with the one or more cytokines described above. In some embodiments, the population of cells is harvested for storage or administration no later than 26 hours after the beginning of contacting the population of cells with the one or more cytokines described above. In some embodiments, the population of cells is harvested for storage or administration no later than 25 hours after the beginning of contacting the population of cells with the one or more cytokines described above. In some embodiments, the population of cells is harvested for storage or administration no later than 24 hours after the beginning of contacting the population of cells with the one or more cytokines described above. In some embodiments, the population of cells is harvested for storage or administration no later than 23 hours after the beginning of contacting the population of cells with the one or more cytokines described above. In some embodiments, the population of cells is harvested for storage or administration no later than 22 hours after the beginning of contacting the population of cells with the one or more cytokines described above.

In some embodiments, the population of cells is not expanded ex vivo.

In some embodiments, the population of cells is expanded by no more than 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 55, or 60%, for example, as assessed by the number of living cells, compared to the population of cells before it is contacted with the one or more cytokines described above. In some embodiments, the population of cells is expanded by no more than 5%, for example, as assessed by the number of living cells, compared to the population of cells before it is contacted with the one or more cytokines described above. In some embodiments, the population of cells is expanded by no more than 10%, for example, as assessed by the number of living cells, compared to the population of cells before it is contacted with the one or more cytokines described above. In some embodiments, the population of cells is expanded by no more than 15%, for example, as assessed by the number of living cells, compared to the population of cells before it is contacted with the one or more cytokines described above. In some embodiments, the population of cells is expanded by no more than 20%, for example, as assessed by the number of living cells, compared to the population of cells before it is contacted with the one or more cytokines described above. In some embodiments, the population of cells is expanded by no more than 25%, for example, as assessed by the number of living cells, compared to the population of cells before it is contacted with the one or

more cytokines described above. In some embodiments, the population of cells is expanded by no more than 30%, for example, as assessed by the number of living cells, compared to the population of cells before it is contacted with the one or more cytokines described above. In some embodiments, the population of cells is expanded by no more than 35%, for example, as assessed by the number of living cells, compared to the population of cells before it is contacted with the one or more cytokines described above. In some embodiments, the population of cells is expanded by no more than 40%, for example, as assessed by the number of living cells, compared to the population of cells before it is contacted with the one or more cytokines described above.

In some embodiments, the population of cells is expanded by no more than 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 9, 10, 11, 12, 16, 20, 24, 36, or 48 hours, for example, as assessed by the number of living cells, compared to the population of cells before it is contacted with the one or more cytokines described above.

In some embodiments, the population of cells is not contacted in vitro with an agent that stimulates a CD3/TCR complex (for example, an anti-CD3 antibody) and/or an agent that stimulates a costimulatory molecule on the surface of the cells (for example, an anti-CD28 antibody), or if contacted, the contacting step is less than 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, or 5 hours.

In some embodiments, the population of cells is contacted in vitro with an agent that stimulates a CD3/TCR complex (for example, an anti-CD3 antibody) and/or an agent that stimulates a costimulatory molecule on the surface of the cells (for example, an anti-CD28 antibody) for 20, 21, 22, 23, 24, 25, 26, 27, or 28 hours.

In some embodiments, the population of cells manufactured using the cytokine process provided herein shows a higher percentage of naïve cells among CAR-expressing cells (for example, at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 55, or 60% higher), compared with cells made by an otherwise similar method which further comprises contacting the population of cells with, for example, an agent that binds a CD3/TCR complex (for example, an anti-CD3 antibody) and/or an agent that binds a costimulatory molecule on the surface of the cells (for example, an anti-CD28 antibody).

In some embodiments, the cytokine process provided herein is conducted in cell media comprising no more than 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, or 8% serum. In some embodiments, the cytokine process provided herein is conducted in cell media comprising a LSD1 inhibitor, a MALT1 inhibitor, or a combination thereof.

#### Additional Exemplary Manufacturing Methods

In some embodiments, cells, e.g., T cells or NK cells are activated, e.g., using anti-CD3/anti-CD28 antibody coated Dynabeads®, contacted with one or more nucleic acid molecules encoding a CAR (e.g. one or more CARs) and then expanded in vitro for, for example, 7, 8, 9, 10, or 11 days. In some embodiments, the cells, e.g., T cells or NK cells are selected from a fresh or cryopreserved leukapheresis sample, e.g., using positive or negative selection. In some embodiments, the cells are contacted with a nucleic acid molecule (e.g. one or more nucleic acid molecules) encoding a CAR (e.g. one or more CARs). In some embodiments, the cells are contacted with a nucleic acid molecule encoding two CARs disclosed herein (e.g., an anti-BCMA CAR and an anti-CD19 CAR). In some embodiments, the cells are

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contacted with two nucleic acid molecules, one expressing a first CAR (e.g., an anti-BCMA CAR) and the other expressing a second CAR (e.g., an anti-CD19 CAR). In some embodiments, the cells are contacted with a nucleic acid molecule encoding a diabody CAR (e.g., an anti-BCMA/anti-CD19 diabody CAR disclosed herein).

## Elutriation

In some embodiments, the methods described herein feature an elutriation method that removes unwanted cells, for example, monocytes and blasts, thereby resulting in an improved enrichment of desired immune effector cells suitable for CAR expression. In some embodiments, the elutriation method described herein is optimized for the enrichment of desired immune effector cells suitable for CAR expression from a previously frozen sample, for example, a thawed sample. In some embodiments, the elutriation method described herein provides a preparation of cells with improved purity as compared to a preparation of cells collected from the elutriation protocols known in the art. In some embodiments, the elutriation method described herein includes using an optimized viscosity of the starting sample, for example, cell sample, for example, thawed cell sample, by dilution with certain isotonic solutions (for example, PBS), and using an optimized combination of flow rates and collection volume for each fraction collected by an elutriation device. Exemplary elutriation methods that could be applied in the present invention are described on pages 48-51 of WO 2017/117112, herein incorporated by reference in its entirety.

## Density Gradient Centrifugation

Manufacturing of adoptive cell therapeutic product requires processing the desired cells, for example, immune effector cells, away from a complex mixture of blood cells and blood elements present in peripheral blood apheresis starting materials. Peripheral blood-derived lymphocyte samples have been successfully isolated using density gradient centrifugation through Ficoll solution. However, Ficoll is not a preferred reagent for isolating cells for therapeutic use, as Ficoll is not qualified for clinical use. In addition, Ficoll contains glycol, which has toxic potential to the cells. Furthermore, Ficoll density gradient centrifugation of thawed apheresis products after cryopreservation yields a suboptimal T cell product, for example, as described in the Examples herein. For example, a loss of T cells in the final product, with a relative gain of non-T cells, especially undesirable B cells, blast cells and monocytes was observed in cell preparations isolated by density gradient centrifugation through Ficoll solution.

Without wishing to be bound by theory, it is believed that immune effector cells, for example, T cells, dehydrate during cryopreservation to become denser than fresh cells. Without wishing to be bound by theory, it is also believed that immune effector cells, for example, T cells, remain denser longer than the other blood cells, and thus are more readily lost during Ficoll density gradient separation as compared to other cells. Accordingly, without wishing to be bound by theory, a medium with a density greater than Ficoll is believed to provide improved isolation of desired immune effector cells in comparison to Ficoll or other mediums with the same density as Ficoll, for example, 1.077 g/mL.

In some embodiments, the density gradient centrifugation method described herein includes the use of a density gradient medium comprising iodixanol. In some embodiments, the density gradient medium comprises about 60% iodixanol in water.

In some embodiments, the density gradient centrifugation method described herein includes the use of a density

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gradient medium having a density greater than Ficoll. In some embodiments, the density gradient centrifugation method described herein includes the use of a density gradient medium having a density greater than 1.077 g/mL, for example, greater than 1.077 g/mL, greater than 1.1 g/mL, greater than 1.15 g/mL, greater than 1.2 g/mL, greater than 1.25 g/mL, greater than 1.3 g/mL, greater than 1.31 g/mL. In some embodiments, the density gradient medium has a density of about 1.32 g/mL.

Additional embodiments of density gradient centrifugation are described on pages 51-53 of WO 2017/117112, herein incorporated by reference in its entirety.

## Enrichment by Selection

Provided herein are methods for selection of specific cells to improve the enrichment of the desired immune effector cells suitable for CAR expression. In some embodiments, the selection comprises a positive selection, for example, selection for the desired immune effector cells. In some embodiments, the selection comprises a negative selection, for example, selection for unwanted cells, for example, removal of unwanted cells. In embodiments, the positive or negative selection methods described herein are performed under flow conditions, for example, by using a flow-through device, for example, a flow-through device described herein. Exemplary positive and negative selections are described on pages 53-57 of WO 2017/117112, herein incorporated by reference in its entirety. Selection methods can be performed under flow conditions, for example, by using a flow-through device, also referred to as a cell processing system, to further enrich a preparation of cells for desired immune effector cells, for example, T cells, suitable for CAR expression. Exemplary flow-through devices are described on pages 57-70 of WO 2017/117112, herein incorporated by reference in its entirety. Exemplary cell separation and debeading methods are described on pages 70-78 of WO 2017/117112, herein incorporated by reference in its entirety.

Selection procedures are not limited to ones described on pages 57-70 of WO 2017/117112. Negative T cell selection via removal of unwanted cells with CD19, CD14 and CD26 Miltenyi beads in combination with column technology (CliniMACS® Plus or ClinIMACS® Prodigy®) or positive T cell selection with a combination of CD4 and CD8 Miltenyi beads and column technology (CliniMACS® Plus or ClinIMACS® Prodigy®) can be used. Alternatively, column-free technology with releasable CD3 beads (GE Healthcare) can be used.

In addition, bead-free technologies such as ThermoGenesis X-series devices can be utilized as well.

## Clinical Applications

All of the processes herein may be conducted according to clinical good manufacturing practice (cGMP) standards.

The processes may be used for cell purification, enrichment, harvesting, washing, concentration or for cell media exchange, particularly during the collection of raw, starting materials (particularly cells) at the start of the manufacturing process, as well as during the manufacturing process for the selection or expansion of cells for cell therapy.

The cells may include any plurality of cells. The cells may be of the same cell type, or mixed cell types. In addition, the cells may be from one donor, such as an autologous donor or a single allogenic donor for cell therapy. The cells may be obtained from patients by, for example, leukapheresis or apheresis. The cells may include T cells, for example may include a population that has greater than 50% T cells, greater than 60% T cells, greater than 70% T cells, greater than 80% T cells, or 90% T cells.

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Selection processes may be particularly useful in selecting cells prior to culture and expansion. For instance, paramagnetic particles coated with anti-CD3 and/or anti CD28 may be used to select T cells for expansion or for introduction of a nucleic acid encoding a chimeric antigen receptor (CAR) or other protein. Such a process is used to produce CTL019 T cells for treatment of acute lymphoblastic leukemia (ALL).

The debeading processes and modules disclosed herein may be particularly useful in the manufacture of cells for cell therapy, for example in purifying cells prior to, or after, culture and expansion. For instance, paramagnetic particles coated with anti-CD3 and/or anti CD28 antibodies may be used to selectively expand T cells, for example T cells that are, or will be, modified by introduction of a nucleic acid encoding a chimeric antigen receptor (CAR) or other protein, such that the CAR is expressed by the T cells. During the manufacture of such T cells, the debeading processes or modules may be used to separate T cells from the paramagnetic particles. Such a debeading process or module is used to produce, for example, CTL019 T cells for treatment of acute lymphoblastic leukemia (ALL).

In one such process, illustrated here by way of example, cells, for example, T cells, are collected from a donor (for example, a patient to be treated with an autologous chimeric antigen receptor T cell product) via apheresis (for example, leukapheresis). Collected cells may then be optionally purified, for example, by an elutriation step, or via positive or negative selection of target cells (for example, T cells). Paramagnetic particles, for example, anti-CD3/anti-CD28-coated paramagnetic particles, may then be added to the cell population, to expand the T cells. The process may also include a transduction step, wherein nucleic acid encoding one or more desired proteins, for example, a CAR, for example a CAR targeting CD19, is introduced into the cell. The nucleic acid may be introduced in a lentiviral vector. The cells, for example, the lentivirally transduced cells, may then be expanded for a period of days, for example, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more days, for example in the presence of a suitable medium. After expansion, the debeading processes/modules disclosed herein may be used to separate the desired T cells from the paramagnetic particles. The process may include one or more debeading steps according to the processes of the present disclosure. The debeaded cells may then be formulated for administration to the patient. Examples of CAR T cells and their manufacture are further described, for example, in WO2012/079000, which is incorporated herein by reference in its entirety. The systems and methods of the present disclosure may be used for any cell separation/purification/debeading processes described in or associated with WO2012/079000. Additional CAR T manufacturing processes are described in, for example, WO2016109410 and WO2017117112, herein incorporated by reference in their entireties.

The systems and methods herein may similarly benefit other cell therapy products by wasting fewer desirable cells, causing less cell trauma, and more reliably removing magnetic and any non-paramagnetic particles from cells with less or no exposure to chemical agents, as compared to conventional systems and methods.

Although only exemplary embodiments of the disclosure are specifically described above, it will be appreciated that modifications and variations of these examples are possible without departing from the spirit and intended scope of the disclosure. For example, the magnetic modules and systems containing them may be arranged and used in a variety of configurations in addition to those described. Besides, non-

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magnetic modules can be utilized as well. In addition, the systems and methods may include additional components and steps not specifically described herein. For instance, methods may include priming, where a fluid is first introduced into a component to remove bubbles and reduce resistance to cell suspension or buffer movement. Furthermore, embodiments may include only a portion of the systems described herein for use with the methods described herein. For example, embodiments may relate to disposable modules, hoses, etc. usable within non-disposable equipment to form a complete system able to separate or debead cells to produce a cell product.

Additional manufacturing methods and processes that can be combined with the present invention have been described in the art. For example, pages 86-91 of WO 2017/117112 describe improved wash steps and improved manufacturing process.

#### Sources of Immune Effector Cells

This section provides additional methods or steps for obtaining an input sample comprising desired immune effector cells, isolating and processing desired immune effector cells, for example, T cells, and removing unwanted materials, for example, unwanted cells. The additional methods or steps described in this section can be used in combination with any of the elutriation, density gradient centrifugation, selection under flow conditions, or improved wash step described in the preceding sections.

A source of cells, for example, T cells or natural killer (NK) cells, can be obtained from a subject. Examples of subjects include humans, monkeys, chimpanzees, dogs, cats, mice, rats, and transgenic species thereof. T cells can be obtained from a number of sources, including peripheral blood mononuclear cells, bone marrow, lymph node tissue, cord blood, thymus tissue, tissue from a site of infection, ascites, pleural effusion, spleen tissue, and tumors.

In some embodiments of the present disclosure, immune effector cells, for example, T cells, can be obtained from a unit of blood collected from a subject using any number of techniques known to the skilled artisan, and any of the methods disclosed herein, in any combination of steps thereof. In some embodiments, cells from the circulating blood of an individual are obtained by apheresis. The apheresis product typically contains lymphocytes, including T cells, monocytes, granulocytes, B cells, other nucleated white blood cells, red blood cells, and platelets. In some embodiments, the cells collected by apheresis may be washed to remove the plasma fraction and, optionally, to place the cells in an appropriate buffer or media for subsequent processing steps. In some embodiments, the cells are washed with phosphate buffered saline (PBS). In some embodiments, the wash solution lacks calcium and may lack magnesium or may lack many if not all divalent cations. In some embodiments, the cells are washed using the improved wash step described herein.

Initial activation steps in the absence of calcium can lead to magnified activation. As those of ordinary skill in the art would readily appreciate a washing step may be accomplished by methods known to those in the art, such as by using a semi-automated "flow-through" centrifuge (for example, the Cobe 2991 cell processor, the Baxter Cyto-Mate™, or the Haemonetics Cell Saver 5), Haemonetics Cell Saver Elite (GE Healthcare Sepax or Sefia), or a device utilizing the spinning membrane filtration technology (Fresenius Kabi LOVO), according to the manufacturer's instructions. After washing, the cells may be resuspended in a variety of biocompatible buffers, such as, for example, Ca-free, Mg-free PBS, PlasmaLyte A, PBS-EDTA supple-

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mented with human serum albumin (HSA), or other saline solution with or without buffer. Alternatively, the undesirable components of the apheresis sample may be removed and the cells directly resuspended in culture media.

In some embodiments, desired immune effector cells, for example, T cells, are isolated from peripheral blood lymphocytes by lysing the red blood cells and depleting the monocytes, for example, by centrifugation through a PER-COLL™ gradient or by counterflow centrifugal elutriation.

The methods described herein can include, for example, selection of a specific subpopulation of immune effector cells, for example, T cells, that are a T regulatory cell-depleted population, for example, CD25+ depleted cells or CD25<sup>high</sup> depleted cells, using, for example, a negative selection technique, for example, described herein. In some embodiments, the population of T regulatory-depleted cells contains less than 30%, 25%, 20%, 15%, 10%, 5%, 4%, 3%, 2%, 1% of CD25+ cells or CD25<sup>high</sup> cells.

In some embodiments, T regulatory cells, for example, CD25+ T cells or CD25<sup>high</sup> T cells, are removed from the population using an anti-CD25 antibody, or fragment thereof, or a CD25-binding ligand, for example IL-2. In some embodiments, the anti-CD25 antibody, or fragment thereof, or CD25-binding ligand is conjugated to a substrate, for example, a bead, or is otherwise coated on a substrate, for example, a bead. In some embodiments, the anti-CD25 antibody, or fragment thereof, is conjugated to a substrate as described herein.

In some embodiments, the T regulatory cells, for example, CD25+ T cells or CD25<sup>high</sup> T cells, are removed from the population using CD25 depleting reagent from Miltenyi™. In some embodiments, the ratio of cells to CD25 depletion reagent is 1e7 cells to 20 µL, or 1e7 cells to 15 µL, or 1e7 cells to 10 µL, or 1e7 cells to 5 µL, or 1e7 cells to 2.5 µL, or 1e7 cells to 1.25 µL. In some embodiments, for example, for T regulatory cells, greater than 500 million cells/ml is used. In some embodiments, a concentration of cells of 600, 700, 800, or 900 million cells/ml is used.

In some embodiments, the population of immune effector cells to be depleted includes about  $6 \times 10^9$  CD25+ T cells. In some embodiments, the population of immune effector cells to be depleted include about  $1 \times 10^9$  to  $1 \times 10^{10}$  CD25+ T cell, and any integer value in between. In some embodiments, the resulting population T regulatory-depleted cells has  $2 \times 10^9$  T regulatory cells, for example, CD25+ cells or CD25<sup>high</sup> cells, or less (for example,  $1 \times 10^9$ ,  $5 \times 10^8$ ,  $1 \times 10^8$ ,  $5 \times 10^7$ ,  $1 \times 10^7$ , or less T regulatory cells).

In some embodiments, the T regulatory cells, for example, CD25+ cells or CD25<sup>high</sup> cells, are removed from the population using the CliniMAC system with a depletion tubing set, such as, for example, tubing 162-01. In some embodiments, the CliniMAC system is run on a depletion setting such as, for example, DEPLETION2.1.

Without wishing to be bound by a particular theory, decreasing the level of negative regulators of immune cells (for example, decreasing the number of unwanted immune cells, for example, Treg cells), in a subject prior to apheresis or during manufacturing of a CAR-expressing cell product significantly reduces the risk of subject relapse. For example, methods of depleting Treg cells are known in the art. Methods of decreasing Treg cells include, but are not limited to, cyclophosphamide, anti-GITR antibody (an anti-GITR antibody described herein), CD25-depletion, and combinations thereof.

In some embodiments, the manufacturing methods comprise reducing the number of (for example, depleting) Treg cells prior to manufacturing of the CAR-expressing cell. For

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example, manufacturing methods comprise contacting the sample, for example, the apheresis sample, with an anti-GITR antibody and/or an anti-CD25 antibody (or fragment thereof, or a CD25-binding ligand), for example, to deplete Treg cells prior to manufacturing of the CAR-expressing cell (for example, T cell, NK cell) product.

Without wishing to be bound by a particular theory, decreasing the level of negative regulators of immune cells (for example, decreasing the number of unwanted immune cells, for example, Treg cells), in a subject prior to apheresis or during manufacturing of a CAR-expressing cell product can reduce the risk of a subject's relapse. In some embodiments, a subject is pre-treated with one or more therapies that reduce Treg cells prior to collection of cells for CAR-expressing cell product manufacturing, thereby reducing the risk of subject relapse to CAR-expressing cell treatment. In some embodiments, methods of decreasing Treg cells include, but are not limited to, administration to the subject of one or more of cyclophosphamide, anti-GITR antibody, CD25-depletion, or a combination thereof. In some embodiments, methods of decreasing Treg cells include, but are not limited to, administration to the subject of one or more of cyclophosphamide, anti-GITR antibody, CD25-depletion, or a combination thereof. Administration of one or more of cyclophosphamide, anti-GITR antibody, CD25-depletion, or a combination thereof, can occur before, during or after an infusion of the CAR-expressing cell product. Administration of one or more of cyclophosphamide, anti-GITR antibody, CD25-depletion, or a combination thereof, can occur before, during or after an infusion of the CAR-expressing cell product.

In some embodiments, the manufacturing methods comprise reducing the number of (for example, depleting) Treg cells prior to manufacturing of the CAR-expressing cell. For example, manufacturing methods comprise contacting the sample, for example, the apheresis sample, with an anti-GITR antibody and/or an anti-CD25 antibody (or fragment thereof, or a CD25-binding ligand), for example, to deplete Treg cells prior to manufacturing of the CAR-expressing cell (for example, T cell, NK cell) product.

In some embodiments, a subject is pre-treated with cyclophosphamide prior to collection of cells for CAR-expressing cell product manufacturing, thereby reducing the risk of subject relapse to CAR-expressing cell treatment (for example, CTL019 treatment). In some embodiments, a subject is pre-treated with an anti-GITR antibody prior to collection of cells for CAR-expressing cell (for example, T cell or NK cell) product manufacturing, thereby reducing the risk of subject relapse to CAR-expressing cell treatment.

In some embodiments, the CAR-expressing cell (for example, T cell, NK cell) manufacturing process is modified to deplete Treg cells prior to manufacturing of the CAR-expressing cell (for example, T cell, NK cell) product (for example, a CTL019 product). In some embodiments, CD25-depletion is used to deplete Treg cells prior to manufacturing of the CAR-expressing cell (for example, T cell, NK cell) product (for example, a CTL019 product).

In some embodiments, the population of cells to be removed are neither the regulatory T cells or tumor cells, but cells that otherwise negatively affect the expansion and/or function of CART cells, for example cells expressing CD14, CD11b, CD33, CD15, or other markers expressed by potentially immune suppressive cells. In some embodiments, such cells are envisioned to be removed concurrently with regulatory T cells and/or tumor cells, or following said depletion, or in another order.

The methods described herein can include more than one selection step, for example, more than one depletion step. Enrichment of a T cell population by negative selection can be accomplished, for example, with a combination of antibodies directed to surface markers unique to the negatively selected cells. One method is cell sorting and/or selection via negative magnetic immunoadherence or flow cytometry that uses a cocktail of monoclonal antibodies directed to cell surface markers present on the cells negatively selected. For example, to enrich for CD4+ cells by negative selection, a monoclonal antibody cocktail can include antibodies to CD14, CD20, CD11b, CD16, HLA-DR, and CD8.

The methods described herein can further include removing cells from the population which express a tumor antigen, for example, a tumor antigen that does not comprise CD25, for example, CD19, CD30, CD38, CD123, CD20, CD14 or CD11b, to thereby provide a population of T regulatory-depleted, for example, CD25+ depleted or CD25<sup>high</sup> depleted, and tumor antigen depleted cells that are suitable for expression of a CAR, for example, a CAR described herein. In some embodiments, tumor antigen expressing cells are removed simultaneously with the T regulatory, for example, CD25+ cells or CD25<sup>high</sup> cells. For example, an anti-CD25 antibody, or fragment thereof, and an anti-tumor antigen antibody, or fragment thereof, can be attached to the same substrate, for example, bead, which can be used to remove the cells or an anti-CD25 antibody, or fragment thereof, or the anti-tumor antigen antibody, or fragment thereof, can be attached to separate beads, a mixture of which can be used to remove the cells. In other embodiments, the removal of T regulatory cells, for example, CD25+ cells or CD25<sup>high</sup> cells, and the removal of the tumor antigen expressing cells is sequential, and can occur, for example, in either order.

Also provided are methods that include removing cells from the population which express a check point inhibitor, for example, a check point inhibitor described herein, for example, one or more of PD1+ cells, LAG3+ cells, and TIM3+ cells, to thereby provide a population of T regulatory-depleted, for example, CD25+ depleted cells, and check point inhibitor depleted cells, for example, PD1+, LAG3+ and/or TIM3+ depleted cells. Exemplary check point inhibitors include PD1, PD-L1, PD-L2, CTLA4, TIM3, CEACAM (for example, CEACAM-1, CEACAM-3 and/or CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 or CD270), KIR, A2aR, MHC class I, MHC class II, GAL9, adenosine, and TGF (for example, TGF beta), for example, as described herein. In some embodiments, check point inhibitor expressing cells are removed simultaneously with the T regulatory, for example, CD25+ cells or CD25<sup>high</sup> cells. For example, an anti-CD25 antibody, or fragment thereof, and an anti-check point inhibitor antibody, or fragment thereof, can be attached to the same bead which can be used to remove the cells, or an anti-CD25 antibody, or fragment thereof, and the anti-check point inhibitor antibody, or fragment there, can be attached to separate beads, a mixture of which can be used to remove the cells. In other embodiments, the removal of T regulatory cells, for example, CD25+ cells or CD25<sup>high</sup> cells, and the removal of the check point inhibitor expressing cells is sequential, and can occur, for example, in either order.

Methods described herein can include a positive selection step. For example, T cells can isolated by incubation with anti-CD3/anti-CD28 (for example, 3x28)-conjugated beads, such as Dynabeads® M-450 CD3/CD28 T, for a time period sufficient for positive selection of the desired T cells. In

some embodiments, the time period is about 30 minutes. In some embodiments, the time period ranges from 30 minutes to 36 hours or longer and all integer values there between. In some embodiments, the time period is at least 1, 2, 3, 4, 5, or 6 hours. In some embodiments, the time period is 10 to 24 hours, for example, 24 hours. Longer incubation times may be used to isolate T cells in any situation where there are few T cells as compared to other cell types, such in isolating tumor infiltrating lymphocytes (TIL) from tumor tissue or from immunocompromised individuals. Further, use of longer incubation times can increase the efficiency of capture of CD8+ T cells. Thus, by simply shortening or lengthening the time T cells are allowed to bind to the CD3/CD28 beads and/or by increasing or decreasing the ratio of beads to T cells (as described further herein), subpopulations of T cells can be preferentially selected for or against at culture initiation or at other time points during the process. Additionally, by increasing or decreasing the ratio of anti-CD3 and/or anti-CD28 antibodies on the beads or other surface, subpopulations of T cells can be preferentially selected for or against at culture initiation or at other desired time points.

In some embodiments, a T cell population can be selected that expresses one or more of IFN- $\gamma$ , TNF $\alpha$ , IL-17A, IL-2, IL-3, IL-4, GM-CSF, IL-10, IL-13, granzyme B, and perforin, or other appropriate molecules, for example, other cytokines. Methods for screening for cell expression can be determined, for example, by the methods described in PCT Publication No.: WO 2013/126712.

For isolation of a desired population of cells by positive or negative selection, the concentration of cells and surface (for example, particles such as beads) can be varied. In some embodiments, it may be desirable to significantly decrease the volume in which beads and cells are mixed together (for example, increase the concentration of cells), to ensure maximum contact of cells and beads. For example, in some embodiments, a concentration of 10 billion cells/ml, 9 billion/ml, 8 billion/ml, 7 billion/ml, 6 billion/ml, or 5 billion/ml is used. In some embodiments, a concentration of 1 billion cells/ml is used. In some embodiments, a concentration of cells from 75, 80, 85, 90, 95, or 100 million cells/ml is used. In some embodiments, concentrations of 125 or 150 million cells/ml can be used.

Using high concentrations can result in increased cell yield, cell activation, and cell expansion. Further, use of high cell concentrations allows more efficient capture of cells that may weakly express target antigens of interest, such as CD28-negative T cells, or from samples where there are many tumor cells present (for example, leukemic blood, tumor tissue, etc.). Such populations of cells may have therapeutic value and would be desirable to obtain. For example, using high concentration of cells allows more efficient selection of CD8+ T cells that normally have weaker CD28 expression.

In some embodiments, it may be desirable to use lower concentrations of cells. By significantly diluting the mixture of T cells and surface (for example, particles such as beads), interactions between the particles and cells is minimized. This selects for cells that express high amounts of desired antigens to be bound to the particles. For example, CD4+ T cells express higher levels of CD28 and are more efficiently captured than CD8+ T cells in dilute concentrations. In some embodiments, the concentration of cells used is  $5 \times 10^6$ /ml. In some embodiments, the concentration used can be from about  $1 \times 10^5$ /ml to  $1 \times 10^6$ /ml, and any integer value in between.

In some embodiments, the cells may be incubated on a rotator for varying lengths of time at varying speeds at either 2-10° C. or at room temperature.

In some embodiments, a plurality of the immune effector cells of the population do not express diacylglycerol kinase (DGK), for example, is DGK-deficient. In some embodiments, a plurality of the immune effector cells of the population do not express Ikaros, for example, is Ikaros-deficient. In some embodiments, a plurality of the immune effector cells of the population do not express DGK and Ikaros, for example, is both DGK and Ikaros-deficient.

T cells for stimulation can also be frozen after a washing step. Wishing not to be bound by theory, the freeze and subsequent thaw step provides a more uniform product by removing granulocytes and to some extent monocytes in the cell population. After the washing step that removes plasma and platelets, the cells may be suspended in a freezing solution. While many freezing solutions and parameters are known in the art and will be useful in this context, one method involves using PBS containing 20% DMSO and 8% human serum albumin, or culture media containing 10% Dextran 40 and 5% Dextrose, 20% Human Serum Albumin and 7.5% DMSO, or 31.25% Plasmalyte-A, 31.25% Dextrose 5%, 0.45% NaCl, 10% Dextran 40 and 5% Dextrose, 20% Human Serum Albumin, and 7.5% DMSO or other suitable cell freezing media containing for example, Hespan and PlasmaLyte A, the cells then are frozen to -80° C. at a rate of 1° per minute and stored in the vapor phase of a liquid nitrogen storage tank. Other methods of controlled freezing may be used as well as uncontrolled freezing immediately at -20° C. or in liquid nitrogen.

In some embodiments, cryopreserved cells are thawed and washed as described herein and allowed to rest for one hour at room temperature prior to activation using the methods of the present invention.

Also contemplated in the context of the invention is the collection of blood samples or apheresis product from a subject at a time period prior to when the expanded cells as described herein might be needed. As such, the source of the cells to be expanded can be collected at any time point necessary, and desired cells, such as T cells, isolated and frozen for later use in immune effector cell therapy for any number of diseases or conditions that would benefit from immune effector cell therapy, such as those described herein. In some embodiments a blood sample or an apheresis is taken from a generally healthy subject. In some embodiments, a blood sample or an apheresis is taken from a generally healthy subject who is at risk of developing a disease, but who has not yet developed a disease, and the cells of interest are isolated and frozen for later use. In some embodiments, the T cells may be expanded, frozen, and used at a later time. In some embodiments, samples are collected from a patient shortly after diagnosis of a particular disease as described herein but prior to any treatments. In some embodiments, the cells are isolated from a blood sample or an apheresis from a subject prior to any number of relevant treatment modalities, including but not limited to treatment with agents such as natalizumab, efalizumab, antiviral agents, chemotherapy, radiation, immunosuppressive agents, such as cyclosporin, azathioprine, methotrexate, mycophenolate, and FK506, antibodies, or other immunoablative agents such as CAMPATH, anti-CD3 antibodies, cytoxan, fludarabine, cyclosporin, FK506, rapamycin, mycophenolic acid, steroids, FR901228, and irradiation.

In some embodiments of the present invention, T cells are obtained from a patient directly following treatment that leaves the subject with functional T cells. In this regard, it

has been observed that following certain cancer treatments, in particular treatments with drugs that damage the immune system, shortly after treatment during the period when patients would normally be recovering from the treatment, the quality of T cells obtained may be optimal or improved for their ability to expand ex vivo. Likewise, following ex vivo manipulation using the methods described herein, these cells may be in a preferred state for enhanced engraftment and in vivo expansion. Thus, it is contemplated within the context of the present invention to collect blood cells, including T cells, dendritic cells, or other cells of the hematopoietic lineage, during this recovery phase. Further, in some embodiments, mobilization (for example, mobilization with GM-CSF) and conditioning regimens can be used to create a condition in a subject wherein repopulation, recirculation, regeneration, and/or expansion of particular cell types is favored, especially during a defined window of time following therapy. Illustrative cell types include T cells, B cells, dendritic cells, and other cells of the immune system.

In some embodiments, the immune effector cells expressing a CAR molecule, for example, a CAR molecule described herein, are obtained from a subject that has received a low, immune enhancing dose of an mTOR inhibitor. In some embodiments, the population of immune effector cells, for example, T cells, to be engineered to express a CAR, are harvested after a sufficient time, or after sufficient dosing of the low, immune enhancing, dose of an mTOR inhibitor, such that the level of PD1 negative immune effector cells, for example, T cells, or the ratio of PD1 negative immune effector cells, for example, T cells/PD1 positive immune effector cells, for example, T cells, in the subject or harvested from the subject has been, at least transiently, increased.

In other embodiments, population of immune effector cells, for example, T cells, which have, or will be engineered to express a CAR, can be treated ex vivo by contact with an amount of an mTOR inhibitor that increases the number of PD1 negative immune effector cells, for example, T cells or increases the ratio of PD1 negative immune effector cells, for example, T cells/PD1 positive immune effector cells, for example, T cells.

It is recognized that the methods of the application can utilize culture media conditions comprising 5% or less, for example 2%, human AB serum, and employ known culture media conditions and compositions, for example those described in Smith et al., "Ex vivo expansion of human T cells for adoptive immunotherapy using the novel Xeno-free CTSTM Immune Cell Serum Replacement" Clinical & Translational Immunology (2015) 4, e31; doi:10.1038/cti.2014.31.

In some embodiments, the methods of the application can utilize media conditions comprising at least about 0.1%, 0.5%, 1.0%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, 5%, 6%, 7%, 8%, 9% or 10% serum. In some embodiments, the media comprises about 0.5%-5%, about 0.5%-4.5%, about 0.5%-4%, about 0.5%-3.5%, about 0.5%-3%, about 0.5%-2.5%, about 0.5%-2%, about 0.5%-1.5%, about 0.5%-1.0%, about 1.0%-5%, about 1.5%-5%, about 2%-5%, about 2.5%-5%, about 3%-5%, about 3.5%-5%, about 4%-5%, or about 4.5%-5% serum. In some embodiments, the media comprises about 0.5% serum. In some embodiments, the media comprises about 0.5% serum. In some embodiments, the media comprises about 1% serum. In some embodiments, the media comprises about 1.5% serum. In some embodiments, the media comprises about 2% serum. In some embodiments, the media comprises about 2.5% serum. In some embodiments, the media comprises about 3.5% serum. In some embodiments, the media comprises about 4.5% serum. In some embodiments, the media comprises about 5.5% serum. In some embodiments, the media comprises about 6.5% serum. In some embodiments, the media comprises about 7.5% serum. In some embodiments, the media comprises about 8.5% serum. In some embodiments, the media comprises about 9.5% serum. In some embodiments, the media comprises about 10.5% serum.

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some embodiments, the media comprises about 3% serum. In some embodiments, the media comprises about 3.5% serum. In some embodiments, the media comprises about 4% serum. In some embodiments, the media comprises about 4.5% serum. In some embodiments, the media comprises about 5% serum. In some embodiments, the serum comprises human serum, e.g., human AB serum. In some embodiments, the serum is human serum that has been allowed to naturally coagulate after collection, e.g., off-the-clot (OTC) serum. In some embodiments, the serum is plasma-derived serum human serum. Plasma-derived serum can be produced by defibrinating pooled human plasma collected in the presence of an anticoagulant, e.g., sodium citrate.

In some embodiments, the methods of the application can utilize culture media conditions comprising serum-free medium. In some embodiments, the serum free medium is OpTmizer<sup>TM</sup> CTST<sup>TM</sup> (LifeTech), Immunocult<sup>TM</sup> XF (Stem-cell technologies), CellGro<sup>TM</sup> (CellGenix), TexMacs<sup>TM</sup> (Miltenyi), Stemline<sup>TM</sup> (Sigma), Xvivo15<sup>TM</sup> (Lonza), PrimeXV<sup>®</sup> (Irvine Scientific), or StemXVivo<sup>®</sup> (RandD systems). The serum-free medium can be supplemented with a serum substitute such as ICSR (immune cell serum replacement) from LifeTech. The level of serum substitute (for example, ICSR) can be, for example, up to 5%, for example, about 1%, 2%, 3%, 4%, or 5%. In some embodiments, the serum-free medium can be supplemented with serum, e.g., human serum, e.g., human AB serum. In some embodiments, the serum is human serum that has been allowed to naturally coagulate after collection, e.g., off-the-clot (OTC) serum. In some embodiments, the serum is plasma-derived human serum. Plasma-derived serum can be produced by defibrinating pooled human plasma collected in the presence of an anticoagulant, e.g., sodium citrate.

In some embodiments, a T cell population is diacylglycerol kinase (DGK)-deficient. DGK-deficient cells include cells that do not express DGK RNA or protein, or have reduced or inhibited DGK activity. DGK-deficient cells can be generated by genetic approaches, for example, administering RNA-interfering agents, for example, siRNA, shRNA, miRNA, to reduce or prevent DGK expression. Alternatively, DGK-deficient cells can be generated by treatment with DGK inhibitors described herein.

In some embodiments, a T cell population is Ikaros-deficient. Ikaros-deficient cells include cells that do not express Ikaros RNA or protein, or have reduced or inhibited Ikaros activity. Ikaros-deficient cells can be generated by genetic approaches, for example, administering RNA-interfering agents, for example, siRNA, shRNA, miRNA, to reduce or prevent Ikaros expression. Alternatively, Ikaros-deficient cells can be generated by treatment with Ikaros inhibitors, for example, lenalidomide.

In embodiments, a T cell population is DGK-deficient and Ikaros-deficient, for example, does not express DGK and Ikaros, or has reduced or inhibited DGK and Ikaros activity. Such DGK and Ikaros-deficient cells can be generated by any of the methods described herein.

In some embodiments, the NK cells are obtained from the subject. In some embodiments, the NK cells are an NK cell line, for example, NK-92 cell line (Conkwest).

#### Allogeneic CAR-Expressing Cells

In embodiments described herein, the immune effector cell can be an allogeneic immune effector cell, for example, T cell or NK cell. For example, the cell can be an allogeneic T cell, for example, an allogeneic T cell lacking expression

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of a functional T cell receptor (TCR) and/or human leukocyte antigen (HLA), for example, HLA class I and/or HLA class II.

A T cell lacking a functional TCR can be, for example, engineered such that it does not express any functional TCR on its surface, engineered such that it does not express one or more subunits that comprise a functional TCR (for example, engineered such that it does not express (or exhibits reduced expression) of TCR alpha, TCR beta, TCR gamma, TCR delta, TCR epsilon, and/or TCR zeta) or engineered such that it produces very little functional TCR on its surface. Alternatively, the T cell can express a substantially impaired TCR, for example, by expression of mutated or truncated forms of one or more of the subunits of the TCR. The term "substantially impaired TCR" means that this TCR will not elicit an adverse immune reaction in a host.

A T cell described herein can be, for example, engineered such that it does not express a functional HLA on its surface.

For example, a T cell described herein, can be engineered such that cell surface expression HLA, for example, HLA class I and/or HLA class II, is downregulated. In some embodiments, downregulation of HLA may be accomplished by reducing or eliminating expression of beta-2 microglobulin (B2M).

In some embodiments, the T cell can lack a functional TCR and a functional HLA, for example, HLA class I and/or HLA class II.

Modified T cells that lack expression of a functional TCR and/or HLA can be obtained by any suitable means, including a knock out or knock down of one or more subunit of TCR or HLA. For example, the T cell can include a knock down of TCR and/or HLA using siRNA, shRNA, clustered regularly interspaced short palindromic repeats (CRISPR) transcription-activator like effector nuclease (TALEN), or zinc finger endonuclease (ZFN).

In some embodiments, the allogeneic cell can be a cell which does not express or expresses at low levels an inhibitory molecule, for example by any method described herein. For example, the cell can be a cell that does not express or expresses at low levels an inhibitory molecule, for example, that can decrease the ability of a CAR-expressing cell to mount an immune effector response. Examples of inhibitory molecules include PD1, PD-L1, PD-L2, CTLA4, TIM3, CEACAM (for example, CEACAM-1, CEACAM-3 and/or CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 or CD270), KIR, A2aR, MHC class I, MHC class II, GAL9, adenosine, and TGF (for example, TGF beta). Inhibition of an inhibitory molecule, for example, by inhibition at the DNA, RNA or protein level, can optimize a CAR-expressing cell performance. In embodiments, an inhibitory nucleic acid, for example, an inhibitory nucleic acid, for example, a dsRNA, for example, an siRNA or shRNA, a clustered regularly interspaced short palindromic repeats (CRISPR), a transcription-activator like effector nuclease (TALEN), or a zinc finger endonuclease (ZFN), for example, as described herein, can be used.

#### siRNA and shRNA to Inhibit TCR or HLA

In some embodiments, TCR expression and/or HLA expression can be inhibited using siRNA or shRNA that targets a nucleic acid encoding a TCR and/or HLA, and/or an inhibitory molecule described herein (for example, PD1, PD-L1, PD-L2, CTLA4, TIM3, CEACAM (for example, CEACAM-1, CEACAM-3 and/or CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CD80, CD86,

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B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 or CD270), KIR, A2aR, MHC class I, MHC class II, GAL9, adenosine, and TGF beta), in a cell, for example, T cell.

Expression systems for siRNA and shRNAs, and exemplary shRNAs, are described, for example, in paragraphs 649 and 650 of International Application WO2015/142675, filed Mar. 13, 2015, which is incorporated by reference in its entirety.

## CRISPR to Inhibit TCR or HLA

“CRISPR” or “CRISPR to TCR and/or HLA” or “CRISPR to inhibit TCR and/or HLA” as used herein refers to a set of clustered regularly interspaced short palindromic repeats, or a system comprising such a set of repeats. “Cas”, as used herein, refers to a CRISPR-associated protein. A “CRISPR/Cas” system refers to a system derived from CRISPR and Cas which can be used to silence or mutate a TCR and/or HLA gene, and/or an inhibitory molecule described herein (for example, PD1, PD-L1, PD-L2, CTLA4, TIM3, CEACAM (for example, CEACAM-1, CEACAM-3 and/or CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 or CD270), KIR, A2aR, MHC class I, MHC class II, GAL9, adenosine, and TGF beta), in a cell, for example, T cell.

The CRISPR/Cas system, and uses thereof, are described, for example, in paragraphs 651-658 of International Application WO2015/142675, filed Mar. 13, 2015, which is incorporated by reference in its entirety.

## TALEN to Inhibit TCR and/or HLA

“TALEN” or “TALEN to HLA and/or TCR” or “TALEN to inhibit HLA and/or TCR” refers to a transcription activator-like effector nuclease, an artificial nuclease which can be used to edit the HLA and/or TCR gene, and/or an inhibitory molecule described herein (for example, PD1, PD-L1, PD-L2, CTLA4, TIM3, CEACAM (for example, CEACAM-1, CEACAM-3 and/or CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 or CD270), KIR, A2aR, MHC class I, MHC class II, GAL9, adenosine, and TGF beta), in a cell, for example, T cell.

TALENs, and uses thereof, are described, for example, in paragraphs 659-665 of International Application WO2015/142675, filed Mar. 13, 2015, which is incorporated by reference in its entirety.

## Zinc Finger Nuclease to Inhibit HLA and/or TCR

“ZFN” or “Zinc Finger Nuclease” or “ZFN to HLA and/or TCR” or “ZFN to inhibit HLA and/or TCR” refer to a zinc finger nuclease, an artificial nuclease which can be used to edit the HLA and/or TCR gene, and/or an inhibitory molecule described herein (for example, PD1, PD-L1, PD-L2, CTLA4, TIM3, CEACAM (for example, CEACAM-1, CEACAM-3 and/or CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 or CD270), KIR, A2aR, MHC class I, MHC class II, GAL9, adenosine, and TGF beta), in a cell, for example, T cell.

ZFNs, and uses thereof, are described, for example, in paragraphs 666-671 of International Application WO2015/142675, filed Mar. 13, 2015, which is incorporated by reference in its entirety.

## Telomerase Expression

Telomeres play a crucial role in somatic cell persistence, and their length is maintained by telomerase (TERT). Telomere length in CLL cells may be very short (Roth et al., “Significantly shorter telomeres in T-cells of patients with ZAP-70+/CD38 chronic lymphocytic leukaemia” British Journal of Haematology, 143, 383-386., Aug. 28 2008), and

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may be even shorter in manufactured CAR-expressing cells, for example, CART19 cells, limiting their potential to expand after adoptive transfer to a patient. Telomerase expression can rescue CAR-expressing cells from replicative exhaustion.

While not wishing to be bound by any particular theory, in some embodiments, a therapeutic T cell has short term persistence in a patient, due to shortened telomeres in the T cell; accordingly, transfection with a telomerase gene can lengthen the telomeres of the T cell and improve persistence of the T cell in the patient. See Carl June, “Adoptive T cell therapy for cancer in the clinic”, Journal of Clinical Investigation, 117:1466-1476 (2007). Thus, in some embodiments, an immune effector cell, for example, a T cell, ectopically expresses a telomerase subunit, for example, the catalytic subunit of telomerase, for example, TERT, for example, hTERT. In some embodiments, this disclosure provides a method of producing a CAR-expressing cell, comprising contacting a cell with a nucleic acid encoding a telomerase subunit, for example, the catalytic subunit of telomerase, for example, TERT, for example, hTERT. The cell may be contacted with the nucleic acid before, simultaneous with, or after being contacted with a construct encoding a CAR.

Telomerase expression may be stable (for example, the nucleic acid may integrate into the cell’s genome) or transient (for example, the nucleic acid does not integrate, and expression declines after a period of time, for example, several days). Stable expression may be accomplished by transfecting or transducing the cell with DNA encoding the telomerase subunit and a selectable marker, and selecting for stable integrants. Alternatively, or in combination, stable expression may be accomplished by site-specific recombination, for example, using the Cre/Lox or FLP/FRT system.

Transient expression may involve transfection or transduction with a nucleic acid, for example, DNA or RNA such as mRNA. In some embodiments, transient mRNA transfection avoids the genetic instability sometimes associated with stable transfection with TERT. Transient expression of exogenous telomerase activity is described, for example, in International Application WO2014/130909, which is incorporated by reference herein in its entirety. In embodiments, mRNA-based transfection of a telomerase subunit is performed according to the messenger RNA Therapeutics™ platform commercialized by Moderna Therapeutics. For instance, the method may be a method described in U.S. Pat. Nos. 8,710,200, 8,822,663, 8,680,069, 8,754,062, 8,664,194, or 8680069.

In some embodiments, hTERT has the amino acid sequence of GenBank Protein ID AAC51724.1 (Meyerson et al., “hEST2, the Putative Human Telomerase Catalytic Subunit Gene, Is Up-Regulated in Tumor Cells and during Immortalization” Cell Volume 90, Issue 4, 22 Aug. 1997, Pages 785-795):

(SEQ ID NO: 284)

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MPRAPRCRAVRSLLRSHYREVLPLATFVRRRLGPQGWRLVQRGDPAAFRA
LVAQCLVCVPWDARPPAAPSFRQVSCLKELVARVLQLRCERGAKNVLA
FGFALLDGARGGPPEAFTTSVRSYLPNTVTDALRGSGAWGLLLRRVGDD
VLVHLLARCALFVLVAPSCAYQVCGPPLYQLGAATQARPPPHASGPRRR
LGCERAWNHHSVREAGVPLGLPAPGARRGGSASRSLPLPKRPRRGAAPE
PERTPVGQGSWAHPGRTGRPSDRGFCVVSPARPAEEATSLEGALSGTRH

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SHPSVGRQHHAGPPSTSRRPPWDTPCPPVYAE<sup>5</sup>TKHFLYSSGDKEQLRP  
 SFLLSSLRPSLTGARRLVETIPLGSRPWM<sup>10</sup>PGTPRRLPRLPQR<sup>15</sup>YQMRPLP  
 FLELLGNHAQC<sup>20</sup>CPYGVLKTHCPLRAAVTPAAGVCAREKPQGSVAAPEEE  
 DTD<sup>25</sup>PRLVQ<sup>28</sup>LLRHSSPQVYGV<sup>30</sup>FVRACLRLVPPGLWGSRHNERRFLRN  
 TKKFISLGKHA<sup>35</sup>KLSLQELTWKMSVRGC<sup>40</sup>AWLRRSPGV<sup>45</sup>GCPVAAEHLRREE  
 ILAKFLH<sup>50</sup>WLM<sup>55</sup>SVYVVELRSFFYVTETTFQKNRLFFYRKSVWSKLQSIG  
 IROHLKRVQ<sup>60</sup>LRELSAEVRQHREARPALLTSRLRFIPKDGLRPIVNMD  
 YVGARTFRREKRAERLTSRVKALFSV<sup>65</sup>N<sup>70</sup>YERARRPG<sup>75</sup>LLGASV<sup>80</sup>GLDDI  
 HRAWRTFVLRVRAQD<sup>85</sup>PPP<sup>90</sup>ELYFV<sup>95</sup>KVDVTGAYDTIPQ<sup>100</sup>QDRL<sup>105</sup>TEVIASIIK<sup>110</sup>P  
 QNTYCV<sup>115</sup>R<sup>120</sup>YAVVQKA<sup>125</sup>AHG<sup>130</sup>HVRKAFKSHV<sup>135</sup>STL<sup>140</sup>DQ<sup>145</sup>PYMRQFV<sup>150</sup>AHLQETS  
 PLRDAV<sup>155</sup>VIEQ<sup>160</sup>QSS<sup>165</sup>LN<sup>170</sup>EASS<sup>175</sup>GL<sup>180</sup>FDV<sup>185</sup>FLRFMCH<sup>190</sup>HA<sup>195</sup>V<sup>200</sup>R<sup>205</sup>I<sup>210</sup>R<sup>215</sup>G<sup>220</sup>K<sup>225</sup>S<sup>230</sup>Y<sup>235</sup>V<sup>240</sup>Q<sup>245</sup>C<sup>250</sup>Q<sup>255</sup>G<sup>260</sup>I<sup>265</sup>P<sup>270</sup>  
 GSIL<sup>275</sup>STLLCSLC<sup>280</sup>LYCG<sup>285</sup>DMEN<sup>290</sup>KL<sup>295</sup>FAG<sup>300</sup>I<sup>305</sup>R<sup>310</sup>D<sup>315</sup>G<sup>320</sup>L<sup>325</sup>L<sup>330</sup>V<sup>335</sup>D<sup>340</sup>F<sup>345</sup>L<sup>350</sup>T<sup>355</sup>H<sup>360</sup>A<sup>365</sup>T<sup>370</sup>H<sup>375</sup>A<sup>380</sup>K<sup>385</sup>T<sup>390</sup>H<sup>395</sup>A<sup>400</sup>L<sup>405</sup>Q<sup>410</sup>Y<sup>415</sup>R<sup>420</sup>F<sup>425</sup>H<sup>430</sup>A<sup>435</sup>C<sup>440</sup>V<sup>445</sup>L<sup>450</sup>Q<sup>455</sup>P<sup>460</sup>F<sup>465</sup>H<sup>470</sup>Q<sup>475</sup>Q<sup>480</sup>W<sup>485</sup>K<sup>490</sup>N<sup>495</sup>P<sup>500</sup>  
 FLRTL<sup>505</sup>VRGVPEYGC<sup>510</sup>VNL<sup>515</sup>RKT<sup>520</sup>VNFP<sup>525</sup>VE<sup>530</sup>DE<sup>535</sup>ALGGT<sup>540</sup>AFV<sup>545</sup>QMPA<sup>550</sup>HGL<sup>555</sup>FP<sup>560</sup>WC<sup>565</sup>  
 GLLL<sup>570</sup>D<sup>575</sup>T<sup>580</sup>LEV<sup>585</sup>QSD<sup>590</sup>YSSY<sup>595</sup>ART<sup>600</sup>SIRASL<sup>605</sup>TFN<sup>610</sup>R<sup>615</sup>GFKAGR<sup>620</sup>NMRR<sup>625</sup>KL<sup>630</sup>FG<sup>635</sup>VL<sup>640</sup>R<sup>645</sup>L<sup>650</sup>Q<sup>655</sup>V<sup>660</sup>N<sup>665</sup>P<sup>670</sup>  
 KCHSL<sup>675</sup>F<sup>680</sup>DL<sup>685</sup>Q<sup>690</sup>V<sup>695</sup>N<sup>700</sup>L<sup>705</sup>Q<sup>710</sup>T<sup>715</sup>C<sup>720</sup>T<sup>725</sup>N<sup>730</sup>I<sup>735</sup>Y<sup>740</sup>K<sup>745</sup>I<sup>750</sup>L<sup>755</sup>Q<sup>760</sup>A<sup>765</sup>Y<sup>770</sup>R<sup>775</sup>F<sup>780</sup>H<sup>785</sup>A<sup>790</sup>C<sup>795</sup>V<sup>800</sup>L<sup>805</sup>Q<sup>810</sup>L<sup>815</sup>P<sup>820</sup>F<sup>825</sup>H<sup>830</sup>Q<sup>835</sup>Q<sup>840</sup>V<sup>845</sup>W<sup>850</sup>K<sup>855</sup>N<sup>860</sup>P<sup>865</sup>  
 TFFLRV<sup>870</sup>ISDTASL<sup>875</sup>CYS<sup>880</sup>IL<sup>885</sup>K<sup>890</sup>AKNAG<sup>895</sup>MSL<sup>900</sup>GAKGA<sup>905</sup>GPL<sup>910</sup>P<sup>915</sup>SEAV<sup>920</sup>Q<sup>925</sup>WL<sup>930</sup>C<sup>935</sup>H<sup>940</sup>Q<sup>945</sup>A<sup>950</sup>F<sup>955</sup>  
 LLKL<sup>960</sup>TRHRV<sup>965</sup>TYV<sup>970</sup>PLL<sup>975</sup>GS<sup>980</sup>L<sup>985</sup>R<sup>990</sup>T<sup>995</sup>Q<sup>1000</sup>LSR<sup>1005</sup>K<sup>1010</sup>L<sup>1015</sup>P<sup>1020</sup>G<sup>1025</sup>T<sup>1030</sup>T<sup>1035</sup>TA<sup>1040</sup>E<sup>1045</sup>A<sup>1050</sup>A<sup>1055</sup>N<sup>1060</sup>P<sup>1065</sup>AL<sup>1070</sup>P<sup>1075</sup>S<sup>1080</sup>D<sup>1085</sup>F<sup>1090</sup>  
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In some embodiments, the hTERT has a sequence at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to the sequence of SEQ ID NO: 284. In some embodiments, the hTERT has a sequence of SEQ ID NO: 284. In some embodiments, the hTERT comprises a deletion (for example, of no more than 5, 10, 15, 20, or 30 amino acids) at the N-terminus, the C-terminus, or both. In some embodiments, the hTERT comprises a transgenic amino acid sequence (for example, of no more than 5, 10, 15, 20, or 30 amino acids) at the N-terminus, the C-terminus, or both.

In some embodiments, the hTERT is encoded by the nucleic acid sequence of GenBank Accession No. AF018167 (Meyerson et al., “hEST2, the Putative Human Telomerase Catalytic Subunit Gene, Is Up-Regulated in Tumor Cells and during Immortalization” Cell Volume 90, Issue 4, 22 Aug. 1997, Pages 785-795).

Activation and Expansion of Immune Effector Cells (for Example, T Cells)

Immune effector cells such as T cells generated or enriched by the methods described herein may be activated and expanded generally using methods as described, for example, in U.S. Pat. Nos. 6,352,694; 6,534,055; 6,905,680; 6,692,964; 5,858,358; 6,887,466; 6,905,681; 7,144,575; 7,067,318; 7,172,869; 7,232,566; 7,175,843; 5,883,223; 6,905,874; 6,797,514; 6,867,041; and U.S. Patent Application Publication No. 20060121005.

Generally, a population of immune effector cells may be expanded by contact with a surface having attached thereto an agent that stimulates a CD3/TCR complex associated signal and a ligand that stimulates a costimulatory molecule on the surface of the T cells. In particular, T cell populations may be stimulated as described herein, such as by contact with an anti-CD3 antibody, or antigen-binding fragment thereof, or an anti-CD2 antibody immobilized on a surface, or by contact with a protein kinase C activator (for example, bryostatin) in conjunction with a calcium ionophore. For

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costimulation of an accessory molecule on the surface of the T cells, a ligand that binds the accessory molecule is used. For example, a population of T cells can be contacted with an anti-CD3 antibody and an anti-CD28 antibody, under conditions appropriate for stimulating proliferation of the T cells. To stimulate proliferation of either CD4+ T cells or CD8+ T cells, an anti-CD3 antibody and an anti-CD28 antibody can be used. Examples of an anti-CD28 antibody include 9.3, B-T3, XR-CD28 (Diaclone, Besançon, France) can be used as can other methods commonly known in the art (Berg et al., Transplant Proc. 30(8):3975-3977, 1998; Haanen et al., J. Exp. Med. 190(9):13191328, 1999; Garland et al., J. Immunol Meth. 227(1-2):53-63, 1999).

In some embodiments, the primary stimulatory signal and the costimulatory signal for the T cell may be provided by different protocols. For example, the agents providing each signal may be in solution or coupled to a surface. When coupled to a surface, the agents may be coupled to the same surface (i.e., in “cis” formation) or to separate surfaces (i.e., 20 in “trans” formation). Alternatively, one agent may be coupled to a surface and the other agent in solution. In some embodiments, the agent providing the costimulatory signal is bound to a cell surface and the agent providing the primary activation signal is in solution or coupled to a 25 surface. In some embodiments, both agents can be in solution. In some embodiments, the agents may be in soluble form, and then cross-linked to a surface, such as a cell expressing Fc receptors or an antibody or other binding agent which will bind to the agents. In this regard, see for 30 example, U.S. Patent Application Publication Nos. 20040101519 and 20060034810 for artificial antigen presenting cells (aAPCs) that are contemplated for use in activating and expanding T cells in the present invention.

In some embodiments, the two agents are immobilized on beads, either on the same bead, i.e., “cis,” or to separate beads, i.e., “trans.” By way of example, the agent providing the primary activation signal is an anti-CD3 antibody or an antigen-binding fragment thereof and the agent providing the costimulatory signal is an anti-CD28 antibody or antigen-binding fragment thereof; and both agents are co-immobilized to the same bead in equivalent molecular amounts. In some embodiments, a 1:1 ratio of each antibody bound to the beads for CD4+ T cell expansion and T cell growth is used. In some embodiments of the present invention, a ratio of anti CD3:CD28 antibodies bound to the beads is used such that an increase in T cell expansion is observed as compared to the expansion observed using a ratio of 1:1. In some embodiments an increase of from about 1 to about 3 fold is observed as compared to the expansion observed using a ratio of 1:1. In some embodiments, the ratio of CD3:CD28 antibody bound to the beads ranges from 100:1 to 1:100 and all integer values there between. In some embodiments, more anti-CD28 antibody is bound to the particles than anti-CD3 antibody, i.e., the ratio of CD3:CD28 is less than one. In some embodiments, the ratio of anti CD28 antibody to anti CD3 antibody bound to the beads is greater than 2:1. In some embodiments, a 1:100 CD3:CD28 ratio of antibody bound to beads is used. In some embodiments, a 1:75 CD3:CD28 ratio of antibody bound to beads is used. In some embodiments, a 1:50 CD3:CD28 ratio of antibody bound to beads is used. In some embodiments, a 1:30 CD3:CD28 ratio of antibody bound to beads is used. In some embodiments, a 1:10 CD3:CD28 ratio of antibody bound to beads is used. In some embodiments, a 1:3 CD3:CD28 ratio of antibody bound to the beads is used. In some embodiments, a 3:1 CD3:CD28 ratio of antibody bound to the beads is used.

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Ratios of particles to cells from 1:500 to 500:1 and any integer values in between may be used to stimulate T cells or other target cells. As those of ordinary skill in the art can readily appreciate, the ratio of particles to cells may depend on particle size relative to the target cell. For example, small sized beads could only bind a few cells, while larger beads could bind many. In some embodiments the ratio of cells to particles ranges from 1:100 to 100:1 and any integer values in-between and in some embodiments the ratio comprises 1:9 to 9:1 and any integer values in between, can also be used to stimulate T cells. The ratio of anti-CD3- and anti-CD28-coupled particles to T cells that result in T cell stimulation can vary as noted above, however certain suitable values include 1:100, 1:50, 1:40, 1:30, 1:20, 1:10, 1:9, 1:8, 1:7, 1:6, 1:5, 1:4, 1:3, 1:2, 1:1, 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1, 10:1, and 15:1 with one suitable ratio being at least 1:1 particles per T cell. In some embodiments, a ratio of particles to cells of 1:1 or less is used. In some embodiments, a suitable particle: cell ratio is 1:5. In some embodiments, the ratio of particles to cells can be varied depending on the day of stimulation. For example, in some embodiments, the ratio of particles to cells is from 1:1 to 10:1 on the first day and additional particles are added to the cells every day or every other day thereafter for up to 10 days, at final ratios of from 1:1 to 1:10 (based on cell counts on the day of addition). In some embodiments, the ratio of particles to cells is 1:1 on the first day of stimulation and adjusted to 1:5 on the third and fifth days of stimulation. In some embodiments, particles are added on a daily or every other day basis to a final ratio of 1:1 on the first day, and 1:5 on the third and fifth days of stimulation. In some embodiments, the ratio of particles to cells is 2:1 on the first day of stimulation and adjusted to 1:10 on the third and fifth days of stimulation. In some embodiments, particles are added on a daily or every other day basis to a final ratio of 1:1 on the first day, and 1:10 on the third and fifth days of stimulation. One of skill in the art will appreciate that a variety of other ratios may be suitable for use in the present invention. In particular, ratios will vary depending on particle size and on cell size and type. In some embodiments, the most typical ratios for use are in the neighborhood of 1:1, 2:1 and 3:1 on the first day.

In some embodiments, the cells, such as T cells, are combined with agent-coated beads, the beads and the cells are subsequently separated, and then the cells are cultured. In some embodiments, prior to culture, the agent-coated beads and cells are not separated but are cultured together. In some embodiments, the beads and cells are first concentrated by application of a force, such as a magnetic force, resulting in increased ligation of cell surface markers, thereby inducing cell stimulation.

By way of example, cell surface proteins may be ligated by allowing paramagnetic beads to which anti-CD3 and anti-CD28 are attached (3×28 beads) to contact the T cells. In some embodiments the cells (for example, 10<sup>4</sup> to 10<sup>7</sup> T cells) and beads (for example, Dynabeads® M-450 CD3/CD28 T paramagnetic beads at a ratio of 1:1) are combined in a buffer, for example PBS (without divalent cations such as, calcium and magnesium). Again, those of ordinary skill in the art can readily appreciate any cell concentration may be used. For example, the target cell may be very rare in the sample and comprise only 0.01% of the sample or the entire sample (i.e., 100%) may comprise the target cell of interest. Accordingly, any cell number is within the context of the present invention. In some embodiments, it may be desirable to significantly decrease the volume in which particles and cells are mixed together (i.e., increase the concentration of cells), to ensure maximum contact of cells and particles. For

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example, in some embodiments, a concentration of about 10 billion cells/ml, 9 billion/ml, 8 billion/ml, 7 billion/ml, 6 billion/ml, 5 billion/ml, or 2 billion cells/ml is used. In some embodiments, greater than 100 million cells/ml is used. In some embodiments, a concentration of cells of 10, 15, 20, 25, 30, 35, 40, 45, or 50 million cells/ml is used. In some embodiments, a concentration of cells from 75, 80, 85, 90, 95, or 100 million cells/ml is used. In some embodiments, concentrations of 125 or 150 million cells/ml can be used. 10 Using high concentrations can result in increased cell yield, cell activation, and cell expansion. Further, use of high cell concentrations allows more efficient capture of cells that may weakly express target antigens of interest, such as CD28-negative T cells. Such populations of cells may have therapeutic value and would be desirable to obtain in some embodiments. For example, using high concentration of cells allows more efficient selection of CD8+ T cells that normally have weaker CD28 expression.

In some embodiments, cells transduced with a nucleic acid encoding a CAR, for example, a CAR described herein, for example, a CD19 CAR described herein, are expanded, for example, by a method described herein. In some embodiments, the cells are expanded in culture for a period of several hours (for example, about 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 18, 21 hours) to about 14 days (for example, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 days). In some embodiments, the cells are expanded for a period of 4 to 9 days. In some embodiments, the cells are expanded for a period of 8 days or less, for example, 7, 6 or 5 days. In some embodiments, 20 the cells are expanded in culture for 5 days, and the resulting cells are more potent than the same cells expanded in culture for 9 days under the same culture conditions. Potency can be defined, for example, by various T cell functions, for example proliferation, target cell killing, cytokine production, activation, migration, surface CAR expression, CAR quantitative PCR, or combinations thereof. In some embodiments, the cells, for example, a CD19 CAR cell described herein, expanded for 5 days show at least a one, two, three or four-fold increase in cells doublings upon antigen stimulation as compared to the same cells expanded in culture for 9 days under the same culture conditions. In some embodiments, the cells, for example, the cells expressing a CD19 CAR described herein, are expanded in culture for 5 days, and the resulting cells exhibit higher proinflammatory cytokine production, for example, IFN-γ and/or GM-CSF levels, as compared to the same cells expanded in culture for 9 days under the same culture conditions. In some embodiments, the cells, for example, a CD19 CAR cell described herein, expanded for 5 days show at least a one, two, three, four, 30 five, ten-fold or more increase in pg/ml of proinflammatory cytokine production, for example, IFN-γ and/or GM-CSF levels, as compared to the same cells expanded in culture for 9 days under the same culture conditions.

Several cycles of stimulation may also be desired such that culture time of T cells can be 60 days or more. Conditions appropriate for T cell culture include an appropriate media (for example, Minimal Essential Media, a-MEM, RPMI Media 1640, AIM-V, DMEM, F-12, or X-vivo 15 (Lonza), X-Vivo 20, OptiMizer, and IMDM) that 40 may contain factors necessary for proliferation and viability, including serum (for example, fetal bovine or human serum), interleukin-2 (IL-2), insulin, IFNγ, IL-4, IL-7, GM-CSF, IL-10, IL-12, IL-15, TGFβ, and TNFα or any other additives for the growth of cells known to the skilled artisan. 50 Other additives for the growth of cells include, but are not limited to, surfactant, plasmanate, and reducing agents such as N-acetyl-cysteine and 2-mercaptoethanol. Media can

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include, but is not limited to RPMI 1640, AIM-V, DMEM, MEM, a-MEM, F-12, X-Vivo 15, X-Vivo 20, OptiMizer, and IMDM with added amino acids, sodium pyruvate, and vitamins, either serum-free or supplemented with an appropriate amount of serum (or plasma) or a defined set of hormones, and/or an amount of cytokine(s) sufficient for the growth and expansion of T cells. Antibiotics, for example, penicillin and streptomycin, are included only in experimental cultures, not in cultures of cells that are to be infused into a subject. The target cells are maintained under conditions necessary to support growth, for example, an appropriate temperature (for example, 37° C.) and atmosphere (for example, air plus 5% CO<sub>2</sub>).

In some embodiments, the cells are expanded in an appropriate media (for example, media described herein) that includes one or more interleukin that result in at least a 200-fold (for example, 200-fold, 250-fold, 300-fold, 350-fold) increase in cells over a 14-day expansion period, for example, as measured by a method described herein such as flow cytometry. In some embodiments, the cells are expanded in the presence IL-15 and/or IL-7 (for example, IL-15 and IL-7).

In embodiments, methods described herein, for example, CAR-expressing cell manufacturing methods, comprise removing T regulatory cells, for example, CD25+ T cells or CD25<sup>high</sup> T cells, from a cell population, for example, using an anti-CD25 antibody, or fragment thereof, or a CD25-binding ligand, IL-2. Methods of removing T regulatory cells, for example, CD25+ T cells or CD25<sup>high</sup> T cells, from a cell population are described herein. In embodiments, the methods, for example, manufacturing methods, further comprise contacting a cell population (for example, a cell population in which T regulatory cells, such as CD25+ T cells or CD25<sup>high</sup> T cells, have been depleted; or a cell population that has previously contacted an anti-CD25 antibody, fragment thereof, or CD25-binding ligand) with IL-15 and/or IL-7. For example, the cell population (for example, that has previously contacted an anti-CD25 antibody, fragment thereof, or CD25-binding ligand) is expanded in the presence of IL-15 and/or IL-7.

In some embodiments a CAR-expressing cell described herein is contacted with a composition comprising a interleukin-15 (IL-15) polypeptide, a interleukin-15 receptor alpha (IL-15Ra) polypeptide, or a combination of both a IL-15 polypeptide and a IL-15Ra polypeptide for example, hetIL-15, during the manufacturing of the CAR-expressing cell, for example, ex vivo. In embodiments, a CAR-expressing cell described herein is contacted with a composition comprising an IL-15 polypeptide during the manufacturing of the CAR-expressing cell, for example, ex vivo. In embodiments, a CAR-expressing cell described herein is contacted with a composition comprising a combination of both an IL-15 polypeptide and a IL-15 Ra polypeptide during the manufacturing of the CAR-expressing cell, for example, ex vivo. In embodiments, a CAR-expressing cell described herein is contacted with a composition comprising hetIL-15 during the manufacturing of the CAR-expressing cell, for example, ex vivo.

In some embodiments the CAR-expressing cell described herein is contacted with a composition comprising hetIL-15 during ex vivo expansion. In some embodiments, the CAR-expressing cell described herein is contacted with a composition comprising an IL-15 polypeptide during ex vivo expansion. In some embodiments, the CAR-expressing cell described herein is contacted with a composition comprising both an IL-15 polypeptide and an IL-15Ra polypeptide during ex vivo expansion. In some embodiments the con-

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tacting results in the survival and proliferation of a lymphocyte subpopulation, for example, CD8+ T cells.

T cells that have been exposed to varied stimulation times may exhibit different characteristics. For example, typical blood or apheresed peripheral blood mononuclear cell products have a helper T cell population (TH, CD4+) that is greater than the cytotoxic or suppressor T cell population (TC, CD8+). Ex vivo expansion of T cells by stimulating CD3 and CD28 receptors produces a population of T cells that prior to about days 8-9 consists predominately of TH cells, while after about days 8-9, the population of T cells comprises an increasingly greater population of TC cells. Accordingly, depending on the purpose of treatment, infusing a subject with a T cell population comprising predominately of TH cells may be advantageous. Similarly, if an antigen-specific subset of TC cells has been isolated it may be beneficial to expand this subset to a greater degree.

Further, in addition to CD4 and CD8 markers, other phenotypic markers vary significantly, but in large part, reproducibly during the course of the cell expansion process. Thus, such reproducibility enables the ability to tailor an activated T cell product for specific purposes.

Once a CAR described herein is constructed, various assays can be used to evaluate the activity of the molecule, such as but not limited to, the ability to expand T cells following antigen stimulation, sustain T cell expansion in the absence of re-stimulation, and anti-cancer activities in appropriate in vitro and animal models. Assays to evaluate the effects of a CAR of the present invention are described in further detail below Western blot analysis of CAR expression in primary T cells can be used to detect the presence of monomers and dimers, for example, as described in paragraph 695 of International Application WO2015/142675, filed Mar. 13, 2015, which is herein incorporated by reference in its entirety.

In vitro expansion of CAR<sup>+</sup> T cells following antigen stimulation can be measured by flow cytometry. For example, a mixture of CD4<sup>+</sup> and CD8<sup>+</sup> T cells are stimulated with αCD3/αCD28 aAPCs followed by transduction with lentiviral vectors expressing GFP under the control of the promoters to be analyzed. Exemplary promoters include the CMV IE gene, EF-1α, ubiquitin C, or phosphoglycerokinase (PGK) promoters. GFP fluorescence is evaluated on day 6 of culture in the CD4<sup>+</sup> and/or CD8<sup>+</sup> T cell subsets by flow cytometry. See, for example, Milone et al., Molecular Therapy 17(8): 1453-1464 (2009). Alternatively, a mixture of CD4<sup>+</sup> and CD8<sup>+</sup> T cells are stimulated with αCD3/αCD28 coated magnetic beads on day 0, and transduced with CAR on day 1 using a bicistronic lentiviral vector expressing CAR along with eGFP using a 2A ribosomal skipping sequence. Cultures are re-stimulated with either a cancer associated antigen as described herein<sup>+</sup> K562 cells (K562-expressing a cancer associated antigen as described herein), wild-type K562 cells (K562 wild type) or K562 cells expressing hCD32 and 4-1BBL in the presence of antiCD3 and anti-CD28 antibody (K562-BBL-3/28). Exogenous IL-2 is added to the cultures every other day at 100 IU/ml. GFP<sup>+</sup> T cells are enumerated by flow cytometry using bead-based counting. See, for example, Milone et al., Molecular Therapy 17(8): 1453-1464 (2009).

Sustained CAR<sup>+</sup> T cell expansion in the absence of re-stimulation can also be measured. See, for example, Milone et al., Molecular Therapy 17(8): 1453-1464 (2009). Briefly, mean T cell volume (fl) is measured on day 8 of culture using a Coulter Multisizer III particle counter or a higher version, a Nexcelom Cellometer Vision, Millipore Scepter or other cell counters, following stimulation with

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$\alpha$ CD3/ $\alpha$ CD28 coated magnetic beads on day 0, and transduction with the indicated CAR on day 1.

Animal models can also be used to measure a CAR-expressing cell activity, for example, as described in paragraph 698 of International Application WO2015/142675, filed Mar. 13, 2015, which is herein incorporated by reference in its entirety.

Dose dependent CAR treatment response can be evaluated, for example, as described in paragraph 699 of International Application WO2015/142675, filed Mar. 13, 2015, which is herein incorporated by reference in its entirety.

Assessment of cell proliferation and cytokine production has been previously described, as described in paragraph 700 of International Application WO2015/142675, filed Mar. 13, 2015, which is herein incorporated by reference in its entirety.

Cytotoxicity can be assessed by a standard  $^{51}\text{Cr}$ -release assay, for example, as described in paragraph 701 of International Application WO2015/142675, filed Mar. 13, 2015, which is herein incorporated by reference in its entirety.

Alternative non-radioactive methods can be utilized as well.

Cytotoxicity can also be assessed by measuring changes in adherent cell's electrical impedance, for example, using an xCELLigence real time cell analyzer (RTCA). In some embodiments, cytotoxicity is measured at multiple time points.

Imaging technologies can be used to evaluate specific trafficking and proliferation of CARs in tumor-bearing animal models, for example, as described in paragraph 702 of International Application WO2015/142675, filed Mar. 13, 2015, which is herein incorporated by reference in its entirety.

Other assays, including those described in the Example section herein as well as those that are known in the art can also be used to evaluate the CARs described herein.

Alternatively, or in combination to the methods disclosed herein, methods and compositions for one or more of: detection and/or quantification of CAR-expressing cells (for example, in vitro or in vivo (for example, clinical monitoring)); immune cell expansion and/or activation; and/or CAR-specific selection, that involve the use of a CAR ligand, are disclosed. In some embodiments, the CAR ligand is an antibody that binds to the CAR molecule, for example, binds to the extracellular antigen binding domain of CAR (for example, an antibody that binds to the antigen binding domain, for example, an anti-idiotypic antibody; or an antibody that binds to a constant region of the extracellular binding domain). In other embodiments, the CAR ligand is a CAR antigen molecule (for example, a CAR antigen molecule as described herein).

In some embodiments, a method for detecting and/or quantifying CAR-expressing cells is disclosed. For example, the CAR ligand can be used to detect and/or quantify CAR-expressing cells in vitro or in vivo (for example, clinical monitoring of CAR-expressing cells in a patient, or dosing a patient). The method includes:

- providing the CAR ligand (optionally, a labelled CAR ligand, for example, a CAR ligand that includes a tag, a bead, a radioactive or fluorescent label);
- acquiring the CAR-expressing cell (for example, acquiring a sample containing CAR-expressing cells, such as a manufacturing sample or a clinical sample);
- contacting the CAR-expressing cell with the CAR ligand under conditions where binding occurs, thereby detecting the level (for example, amount) of the CAR-expressing cells present. Binding of the CAR-express-

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ing cell with the CAR ligand can be detected using standard techniques such as FACS, ELISA and the like.

In some embodiments, a method of expanding and/or activating cells (for example, immune effector cells) is disclosed. The method includes:

- providing a CAR-expressing cell (for example, a first CAR-expressing cell or a transiently expressing CAR cell);

- contacting said CAR-expressing cell with a CAR ligand, for example, a CAR ligand as described herein), under conditions where immune cell expansion and/or proliferation occurs, thereby producing the activated and/or expanded cell population.

In certain embodiments, the CAR ligand is present on a substrate (for example, is immobilized or attached to a substrate, for example, a non-naturally occurring substrate). In some embodiments, the substrate is a non-cellular substrate. The non-cellular substrate can be a solid support chosen from, for example, a plate (for example, a microtiter plate), a membrane (for example, a nitrocellulose membrane), a matrix, a chip or a bead. In embodiments, the CAR ligand is present in the substrate (for example, on the substrate surface). The CAR ligand can be immobilized, attached, or associated covalently or non-covalently (for example, cross-linked) to the substrate. In some embodiments, the CAR ligand is attached (for example, covalently attached) to a bead. In the aforesaid embodiments, the immune cell population can be expanded in vitro or ex vivo. The method can further include culturing the population of immune cells in the presence of the ligand of the CAR molecule, for example, using any of the methods described herein.

In other embodiments, the method of expanding and/or activating the cells further comprises addition of a second stimulatory molecule, for example, CD28. For example, the CAR ligand and the second stimulatory molecule can be immobilized to a substrate, for example, one or more beads, thereby providing increased cell expansion and/or activation.

In some embodiments, a method for selecting or enriching for a CAR expressing cell is provided. The method includes contacting the CAR expressing cell with a CAR ligand as described herein; and selecting the cell on the basis of binding of the CAR ligand.

In yet other embodiments, a method for depleting, reducing and/or killing a CAR expressing cell is provided. The method includes contacting the CAR expressing cell with a CAR ligand as described herein; and targeting the cell on the basis of binding of the CAR ligand, thereby reducing the number, and/or killing, the CAR-expressing cell. In some embodiments, the CAR ligand is coupled to a toxic agent (for example, a toxin or a cell ablative drug). In some embodiments, the anti-idiotypic antibody can cause effector cell activity, for example, ADCC or ADC activities.

Exemplary anti-CAR antibodies that can be used in the methods disclosed herein are described, for example, in WO 2014/190273 and by Jena et al., "Chimeric Antigen Receptor (CAR)-Specific Monoclonal Antibody to Detect CD19-Specific T cells in Clinical Trials", PLOS March 2013 8:3 e57838, the contents of which are incorporated by reference.

In some embodiments, the compositions and methods herein are optimized for a specific subset of T cells, for example, as described in US Serial No. PCT/US2015/043219 filed Jul. 31, 2015, the contents of which are incorporated herein by reference in their entirety. In some embodiments, the optimized subsets of T cells display an enhanced persistence compared to a control T cell, for

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example, a T cell of a different type (for example, CD8+ or CD4+) expressing the same construct.

In some embodiments, a CD4+ T cell comprises a CAR described herein, which CAR comprises an intracellular signaling domain suitable for (for example, optimized for, for example, leading to enhanced persistence in) a CD4+ T cell, for example, an ICOS domain. In some embodiments, a CD8+ T cell comprises a CAR described herein, which CAR comprises an intracellular signaling domain suitable for (for example, optimized for, for example, leading to enhanced persistence of) a CD8+ T cell, for example, a 4-1BB domain, a CD28 domain, or another costimulatory domain other than an ICOS domain. In some embodiments, the CAR described herein comprises an antigen binding domain described herein, for example, a CAR comprising an antigen binding domain.

In some embodiments, described herein is a method of treating a subject, for example, a subject having cancer. The method includes administering to said subject, an effective amount of:

- 1) a CD4+ T cell comprising a CAR (the CARCD4+) comprising:
    - an antigen binding domain, for example, an antigen binding domain described herein;
    - a transmembrane domain; and
    - an intracellular signaling domain, for example, a first costimulatory domain, for example, an ICOS domain; and
  - 2) a CD8+ T cell comprising a CAR (the CARCD8+) comprising:
    - an antigen binding domain, for example, an antigen binding domain described herein;
    - a transmembrane domain; and
    - an intracellular signaling domain, for example, a second costimulatory domain, for example, a 4-1BB domain, a CD28 domain, or another costimulatory domain other than an ICOS domain;
- wherein the CARCD4+ and the CARCD8+ differ from one another.

Optionally, the method further includes administering:

- 3) a second CD8+ T cell comprising a CAR (the second CARCD8+) comprising:
  - an antigen binding domain, for example, an antigen binding domain described herein;
  - a transmembrane domain; and
  - an intracellular signaling domain, wherein the second CARCD8+ comprises an intracellular signaling domain, for example, a costimulatory signaling domain, not present on the CARCD8+, and, optionally, does not comprise an ICOS signaling domain.

#### Biopolymer Delivery Methods

In some embodiments, one or more CAR-expressing cells as disclosed herein can be administered or delivered to the subject via a biopolymer scaffold, for example, a biopolymer implant. Biopolymer scaffolds can support or enhance the delivery, expansion, and/or dispersion of the CAR-expressing cells described herein. A biopolymer scaffold comprises a biocompatible (for example, does not substantially induce an inflammatory or immune response) and/or a biodegradable polymer that can be naturally occurring or synthetic. Exemplary biopolymers are described, for example, in paragraphs 1004-1006 of International Application WO2015/142675, filed Mar. 13, 2015, which is herein incorporated by reference in its entirety.

#### Pharmaceutical Compositions and Treatments

In some embodiments, the disclosure provides a method of treating a patient, comprising administering CAR-ex-

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pressing cells produced as described herein, optionally in combination with one or more other therapies. In some embodiments, the disclosure provides a method of treating a patient, comprising administering a reaction mixture comprising CAR-expressing cells as described herein, optionally in combination with one or more other therapies. In some embodiments, the disclosure provides a method of shipping or receiving a reaction mixture comprising CAR-expressing cells as described herein. In some embodiments, the disclosure provides a method of treating a patient, comprising receiving a CAR-expressing cell that was produced as described herein, and further comprising administering the CAR-expressing cell to the patient, optionally in combination with one or more other therapies. In some embodiments, the disclosure provides a method of treating a patient, comprising producing a CAR-expressing cell as described herein, and further comprising administering the CAR-expressing cell to the patient, optionally in combination with one or more other therapies. The other therapy may be, for example, a cancer therapy such as chemotherapy.

In some embodiments, cells expressing a CAR described herein are administered to a subject in combination with a molecule that decreases the Treg cell population. Methods that decrease the number of (for example, deplete) Treg cells are known in the art and include, for example, CD25 depletion, cyclophosphamide administration, modulating GITR function. Without wishing to be bound by theory, it is believed that reducing the number of Treg cells in a subject prior to apheresis or prior to administration of a CAR-expressing cell described herein reduces the number of unwanted immune cells (for example, Tregs) in the tumor microenvironment and reduces the subject's risk of relapse.

In some embodiments, a therapy described herein, for example, a CAR-expressing cell, is administered to a subject in combination with a molecule targeting GITR and/or modulating GITR functions, such as a GITR agonist and/or a GITR antibody that depletes regulatory T cells (Tregs). In embodiments, cells expressing a CAR described herein are administered to a subject in combination with cyclophosphamide. In some embodiments, the GITR binding molecules and/or molecules modulating GITR functions (for example, GITR agonist and/or Treg depleting GITR antibodies) are administered prior to the CAR-expressing cell. For example, in some embodiments, a GITR agonist can be administered prior to apheresis of the cells. In embodiments, cyclophosphamide is administered to the subject prior to administration (for example, infusion or re-infusion) of the CAR-expressing cell or prior to apheresis of the cells. In embodiments, cyclophosphamide and an anti-GITR antibody are administered to the subject prior to administration (for example, infusion or re-infusion) of the CAR-expressing cell or prior to apheresis of the cells. In some embodiments, the subject has cancer (for example, a solid cancer or a hematological cancer such as ALL or CLL). In some embodiments, the subject has CLL. In embodiments, the subject has ALL. In embodiments, the subject has a solid cancer, for example, a solid cancer described herein. Exemplary GITR agonists include, for example, GITR fusion proteins and anti-GITR antibodies (for example, bivalent anti-GITR antibodies) such as, for example, a GITR fusion protein described in U.S. Pat. No. 6,111,090, European Patent No.: 090505B1, U.S. Pat. No. 8,586,023, PCT Publication Nos.: WO 2010/003118 and 2011/090754, or an anti-GITR antibody described, for example, in U.S. Pat. No. 7,025,962, European Patent No.: 1947183B1, U.S. Pat. Nos. 7,812,135, 8,388,967, 8,591,886, European Patent No.: EP 1866339, PCT Publication No.: WO 2011/028683, PCT

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Publication No.: WO 2013/039954, PCT Publication No.: WO2005/007190, PCT Publication No.: WO 2007/133822, PCT Publication No.: WO2005/055808, PCT Publication No.: WO 99/40196, PCT Publication No.: WO 2001/03720, PCT Publication No.: WO99/20758, PCT Publication No.: WO2006/083289, PCT Publication No.: WO 2005/115451, U.S. Pat. No. 7,618,632, and PCT Publication No.: WO 2011/051726.

In some embodiments, a CAR expressing cell described herein is administered to a subject in combination with a GITR agonist, for example, a GITR agonist described herein. In some embodiments, the GITR agonist is administered prior to the CAR-expressing cell. For example, in some embodiments, the GITR agonist can be administered prior to apheresis of the cells. In some embodiments, the subject has CLL.

The methods described herein can further include formulating a CAR-expressing cell in a pharmaceutical composition. Pharmaceutical compositions may comprise a CAR-expressing cell, for example, a plurality of CAR-expressing cells, as described herein, in combination with one or more pharmaceutically or physiologically acceptable carriers, diluents or excipients. Such compositions may comprise buffers such as neutral buffered saline, phosphate buffered saline and the like; carbohydrates such as glucose, mannose, sucrose or dextran, mannitol; proteins; polypeptides or amino acids such as glycine; antioxidants; chelating agents such as EDTA or glutathione; adjuvants (for example, aluminum hydroxide); and preservatives. Compositions can be formulated, for example, for intravenous administration.

In some embodiments, the pharmaceutical composition is substantially free of, for example, there are no detectable levels of a contaminant, for example, selected from the group consisting of endotoxin, mycoplasma, replication competent lentivirus (RCL), p24, VSV-G nucleic acid, HIV gag, residual anti-CD3/anti-CD28 coated beads, mouse antibodies, pooled human serum, bovine serum albumin, bovine serum, culture media components, vector packaging cell or plasmid components, a bacterium and a fungus. In some embodiments, the bacterium is at least one selected from the group consisting of *Alcaligenes faecalis*, *Candida albicans*, *Escherichia coli*, *Haemophilus influenzae*, *Neisseria meningitidis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Streptococcus pyogenes* group A.

When “an immunologically effective amount,” “an anti-cancer effective amount,” “a cancer-inhibiting effective amount,” or “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). It can generally be stated that a pharmaceutical composition comprising the immune effector cells (for example, T cells, NK cells) described herein may be administered at a dosage of  $10^4$  to  $10^9$  cells/kg body weight, in some instances  $10^5$  to  $10^6$  cells/kg body weight, including all integer values within those ranges. T cell 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, for example, Rosenberg et al., New Eng. J. of Med. 319:1676, 1988).

Exemplary BCMA/CD19 CART Pharmaceutical Compositions

In some embodiments a BCMA/CD19 dual CART cell composition is produced by co-transduction with two unique vectors. Accordingly, in some embodiments, the cell com-

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position comprises a heterogeneous population of cells. In some embodiments, the heterogeneous cell composition includes untransduced T cells, mono BCMA-specific CART cells, mono CD19-specific CART cells, and dual CART cells expressing both BCMA-specific CAR molecules and CD19-specific CAR molecules. These distinct cell populations may exhibit different activities in the context of treating a disease in a subject.

Without wishing to be bound by theory, in the context of treating multiple myeloma, for example, activation of BCMA-specific CART cells can be a main factor in the anti-tumor response in patients, while CD19-specific activity can play a role in eliminating less-prevalent CD19-positive tumor cells.

In some embodiments, the cell composition can be evaluated to assess the relative percentages of the four distinct cell populations, e.g., to select a cell composition that contains a greater percentage of BCMA-specific CAR cells (e.g., mono BCMA-specific CAR cells and BCMA/CD19 dual CAR cells) than mono CD19-specific CAR cells.

In some embodiments, the cell composition comprises:

- (a) a first population of cells comprising an anti-BCMA CAR but not an anti-CD19 CAR;
- (b) a second population of cells comprising an anti-CD19 CAR but not an anti-BCMA CAR; and
- (c) a third population of cells comprising both an anti-BCMA CAR and an anti-CD19 CAR.

In some embodiments:

- (i) the total number of viable cells in the second and third populations combined is less than or equal to about 110% (e.g., less than or equal to about 105%, 100%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, 5%, 1%, or less) of the total number of viable cells in the first and third populations combined;
- (ii) the total number of viable cells in the first and third populations combined is greater than or equal to about 90% (e.g., greater than or equal to about 100%, 125%, 150%, 175%, 200%, 250%, 300%, 400%, 500%, 750%, 1000%, 2000%, 5000, 10000% or more) of the total number of viable cells in the second and third populations combined; and/or
- (iii) the total number of viable cells in the first and third populations combined is greater than or equal to about 5% (e.g., greater than or equal to about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90%) of the total number of viable cells in the population.

In some embodiments, the cell composition further comprises a fourth population of cells that do not comprise a CAR. In some embodiments, the cell composition comprises a population of mono CD19-specific CAR cells that are less than or equal to 110% (e.g., less than or equal to about 105%, 100%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, 5%, 1%, or less) of the number of BCMA-specific CAR cells (e.g., the total number of mono BCMA-specific CAR cells and BCMA/CD19 dual CAR cells). In some embodiments, the cell composition comprises a population of mono CD19 CAR+ cells that comprise about 45% to about 50% (e.g., about 47%) of the number of BCMA-specific CART cells. In some embodiments, the cell composition comprises a population of mono CD19 CAR+ cells that comprise about 60% to about 65% (e.g., about 63%) of the number of BCMA-specific CART cells. In some embodiments, the cell composition comprises a population of mono CD19 CAR+ cells that comprise about 50% to about 55% (e.g., about 53%) of the number of BCMA-specific CART cells. In some embodiments, the cell composition comprises

a population of mono CD19 CAR+ cells that comprise about 82% of the number of BCMA-specific CART cells.

In some embodiments, the cell composition can be evaluated to assess the percentage of CAR-positive viable cells to allow for sufficient dosing. Accordingly, in some embodiments, the cell composition comprises a population of BCMA-specific CAR cells (e.g., the total number of mono BCMA-specific CAR cells and BCMA/CD19 dual CAR cells) that are greater than or equal to about 5% (e.g., greater than or equal to about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 99%, or 100%) of the total number of viable cells in the cell composition.

In some embodiments, the BCMA-specific CAR cells are BCMA-specific CART cells. In some embodiments, the mono BCMA-specific CAR cells are mono BCMA-specific CART cells. In some embodiments, the CD19-specific CAR cells are CD19-specific CART cells. In some embodiments, the mono CD19-specific CAR cells are mono CD19-specific CART cells. In some embodiments, the BCMA/CD19 dual CAR cells are BCMA/CD19 dual CART cells.

#### Dosing

In some embodiments, a dose of CAR cells (for example, CD19 CAR cells) comprises about  $1 \times 10^6$ ,  $1.1 \times 10^6$ ,  $2 \times 10^6$ ,  $3.6 \times 10^6$ ,  $5 \times 10^6$ ,  $1 \times 10^7$ ,  $1.8 \times 10^7$ ,  $2 \times 10^7$ ,  $5 \times 10^7$ ,  $1 \times 10^8$ ,  $2 \times 10^8$ , or  $5 \times 10^8$  cells/kg. In some embodiments, a dose of CAR cells (for example, CD19 CAR cells) comprises at least about  $1 \times 10^6$ ,  $1.1 \times 10^6$ ,  $2 \times 10^6$ ,  $3.6 \times 10^6$ ,  $5 \times 10^6$ ,  $1 \times 10^7$ ,  $1.8 \times 10^7$ ,  $2 \times 10^7$ ,  $5 \times 10^7$ ,  $1 \times 10^8$ ,  $2 \times 10^8$ , or  $5 \times 10^8$  cells/kg. In some embodiments, a dose of CAR cells (for example, CD19 CAR cells) comprises up to about  $1 \times 10^6$ ,  $1.1 \times 10^6$ ,  $2 \times 10^6$ ,  $3.6 \times 10^6$ ,  $5 \times 10^6$ ,  $1 \times 10^7$ ,  $1.8 \times 10^7$ ,  $2 \times 10^7$ ,  $5 \times 10^7$ ,  $1 \times 10^8$ ,  $2 \times 10^8$ , or  $5 \times 10^8$  cells/kg. In some embodiments, a dose of CAR cells (for example, CD19 CAR cells) comprises about  $1.1 \times 10^6$ - $1.8 \times 10^7$  cells/kg. In some embodiments, a dose of CAR cells (for example, CD19 CAR cells) comprises about  $1 \times 10^7$ ,  $2 \times 10^7$ ,  $5 \times 10^7$ ,  $1 \times 10^8$ ,  $2 \times 10^8$ ,  $5 \times 10^8$ ,  $1 \times 10^9$ ,  $2 \times 10^9$ , or  $5 \times 10^9$  cells. In some embodiments, a dose of CAR cells (for example, CD19 CAR cells) comprises at least about  $1 \times 10^7$ ,  $2 \times 10^7$ ,  $5 \times 10^7$ ,  $1 \times 10^8$ ,  $2 \times 10^8$ ,  $5 \times 10^8$ ,  $1 \times 10^9$ ,  $2 \times 10^9$ , or  $5 \times 10^9$  cells. In some embodiments, a dose of CAR cells (for example, CD19 CAR cells) comprises up to about  $1 \times 10^7$ ,  $2 \times 10^7$ ,  $5 \times 10^7$ ,  $1 \times 10^8$ ,  $2 \times 10^8$ ,  $5 \times 10^8$ ,  $1 \times 10^9$ ,  $2 \times 10^9$ , or  $5 \times 10^9$  cells.

In some embodiments, it may be desired to administer activated immune effector cells (for example, T cells, NK cells) to a subject and then subsequently redraw blood (or have an apheresis performed), activate immune effector cells (for example, T cells, NK cells) therefrom, and reinfuse the patient with these activated and expanded immune effector cells (for example, T cells, NK cells). This process can be carried out multiple times every few weeks. In some embodiments, immune effector cells (for example, T cells, NK cells) can be activated from blood draws of from 10cc to 400cc. In some embodiments, immune effector cells (for example, T cells, NK cells) are activated from blood draws of 20cc, 30cc, 40cc, 50cc, 60cc, 70cc, 80cc, 90cc, or 100cc.

The administration of the subject compositions may be carried out in any convenient manner. The compositions described herein may be administered to a patient trans arterially, subcutaneously, intradermally, intratumorally, intranodally, intramedullary, intramuscularly, by intravenous (i.v.) injection, or intraperitoneally, for example, by intradermal or subcutaneous injection. The compositions of immune effector cells (for example, T cells, NK cells) may be injected directly into a tumor, lymph node, or site of infection.

#### T Cell Depletion

In some embodiments, the methods disclosed herein further include administering a T cell depleting agent after treatment with the cell (for example, an immune effector cell as described herein), thereby reducing (for example, depleting) the CAR-expressing cells (for example, the CD19CAR-expressing cells). Such T cell depleting agents can be used to effectively deplete CAR-expressing cells (for example, CD19CAR-expressing cells) to mitigate toxicity. In some 5 embodiments, the CAR-expressing cells were manufactured according to a method herein, for example, assayed (for example, before or after transfection or transduction) according to a method herein.

In some embodiments, the T cell depleting agent is 10 administered one, two, three, four, or five weeks after administration of the cell, for example, the population of immune effector cells, described herein.

In some embodiments, the T cell depleting agent is an 15 agent that depletes CAR-expressing cells, for example, by inducing antibody dependent cell-mediated cytotoxicity (ADCC) and/or complement-induced cell death. For example, CAR-expressing cells described herein may also express an antigen (for example, a target antigen) that is recognized by molecules capable of inducing cell death, for example, ADCC or complement-induced cell death. For example, CAR expressing cells described herein may also express a target protein (for example, a receptor) capable of being targeted by an antibody or antibody fragment. Examples of such target proteins include, but are not limited to, EpCAM, VEGFR, integrins (for example, integrins  $\alpha v \beta 3$ ,  $\alpha 4$ ,  $\alpha 1 \beta 4 \beta 3$ ,  $\alpha 4 \beta 7$ ,  $\alpha 5 \beta 1$ ,  $\alpha v \beta 3$ ,  $\alpha v$ ), members of the TNF receptor superfamily (for example, TRAIL-R1, TRAIL-R2), PDGF Receptor, interferon receptor, folate receptor, GPNMB, ICAM-1, HLA-DR, CEA, CA-125, MUC1, TAG-72, IL-6 receptor, ST4, GD2, GD3, CD2, CD3, CD4, CD5, CD11, CD11a/LFA-1, CD15, CD18/ITGB2, CD19, CD20, CD22, CD23/IgE Receptor, CD25, CD28, CD30, CD33, CD38, CD40, CD41, CD44, CD51, CD52, CD62L, CD74, CD80, CD125, CD147/basigin, CD152/CTLA-4, CD154/CD40L, CD195/CCR5, CD319/SLAMF7, and EGFR, and truncated versions thereof (for example, versions preserving one or more extracellular epitopes but lacking one or more regions within the cytoplasmic domain).

In some embodiments, the CAR expressing cell co-expresses the CAR and the target protein, for example, naturally expresses the target protein or is engineered to express the target protein. For example, the cell, for example, the population of immune effector cells, can include a nucleic acid (for example, vector) comprising the CAR nucleic acid (for example, a CAR nucleic acid as described herein) and a nucleic acid encoding the target protein.

In some embodiments, the T cell depleting agent is a 45 CD52 inhibitor, for example, an anti-CD52 antibody molecule, for example, alemtuzumab.

In other embodiments, the cell, for example, the population of immune effector cells, expresses a CAR molecule as 50 described herein (for example, CD19CAR) and the target protein recognized by the T cell depleting agent. In some embodiments, the target protein is CD20. In embodiments where the target protein is CD20, the T cell depleting agent is an anti-CD20 antibody, for example, rituximab.

In further embodiments of any of the aforesaid methods, 55 the methods further include transplanting a cell, for example, a hematopoietic stem cell, or a bone marrow, into the mammal.

In some embodiments, the invention features a method of conditioning a mammal prior to cell transplantation. The method includes administering to the mammal an effective amount of the cell comprising a CAR nucleic acid or polypeptide, for example, a CD19 CAR nucleic acid or polypeptide.

In some embodiments, the cell transplantation is a stem cell transplantation, for example, a hematopoietic stem cell transplantation, or a bone marrow transplantation. In other embodiments, conditioning a subject prior to cell transplantation includes reducing the number of target-expressing cells in a subject, for example, CD19-expressing normal cells or CD19-expressing cancer cells.

#### Dosage Regimen

In some embodiments, a dose of viable CAR-expressing cells (for example, viable CD19, BCMA, CD20, or CD22 CAR-expressing cells) or a pharmaceutical composition comprising said cells comprises about  $1 \times 10^6$  to about  $1 \times 10^8$  (e.g., about  $2 \times 10^6$  to about  $5 \times 10^7$ , about  $5 \times 10^6$  to about  $2 \times 10^7$ , about  $1 \times 10^6$  to about  $1 \times 10^7$ , about  $1 \times 10^7$  to about  $1 \times 10^8$ , about  $1 \times 10^6$  to about  $3 \times 10^6$ , about  $2 \times 10^6$  to about  $4 \times 10^6$ , about  $3 \times 10^6$  to about  $5 \times 10^6$ , about  $4 \times 10^6$  to about  $6 \times 10^6$ , about  $5 \times 10^6$  to about  $7 \times 10^6$ , about  $6 \times 10^6$  to about  $8 \times 10^6$ , about  $7 \times 10^6$ , about  $8 \times 10^6$  to about  $8 \times 10^6$ , about  $7 \times 10^6$  to about  $9 \times 10^6$ , about  $8 \times 10^6$  to about  $1 \times 10^7$ , about  $1 \times 10^6$  to about  $1 \times 10^7$ , about  $9 \times 10^6$  to about  $2 \times 10^7$ , about  $1 \times 10^7$ , about  $1 \times 10^6$  to about  $3 \times 10^7$ , about  $2 \times 10^7$  to about  $4 \times 10^7$ , about  $3 \times 10^7$  to about  $5 \times 10^7$ , about  $4 \times 10^7$  to about  $6 \times 10^7$ , about  $5 \times 10^7$  to about  $7 \times 10^7$ , about  $6 \times 10^7$  to about  $8 \times 10^7$ , about  $7 \times 10^7$  to about  $9 \times 10^7$ , about  $8 \times 10^7$  to about  $1 \times 10^8$ , about  $1 \times 10^6$  to about  $2 \times 10^6$ , about  $3 \times 10^6$ , about  $4 \times 10^6$ , about  $5 \times 10^6$ , about  $6 \times 10^6$ , about  $7 \times 10^6$ , about  $8 \times 10^6$ , about  $9 \times 10^6$ , about  $1 \times 10^7$ , about  $2 \times 10^7$ , about  $3 \times 10^7$ , about  $4 \times 10^7$ , about  $5 \times 10^7$ , about  $6 \times 10^7$ , about  $7 \times 10^7$ , about  $8 \times 10^7$ , about  $9 \times 10^7$ , or about  $1 \times 10^8$ ) CAR-positive viable cells (e.g., BCMA CAR+ T cells). In some embodiments, a dose of viable CAR-expressing cells (for example, viable CD19, BCMA, CD20, or CD22 CAR-expressing cells) comprises about  $0.5 \times 10^6$  viable CAR-expressing cells to about  $1.25 \times 10^9$  viable CAR-expressing cells (for example,  $0.5 \times 10^6$  viable CAR-expressing cells to  $1.25 \times 10^9$  viable CAR-expressing cells). In some embodiments, a dose of viable CAR-expressing cells (for example, viable CD19, BCMA, CD20, or CD22 CAR-expressing cells) comprises about  $1 \times 10^6$ , about  $2.5 \times 10^6$ , about  $5 \times 10^6$ , about  $1.25 \times 10^7$ , about  $2.5 \times 10^7$ , about  $5 \times 10^7$ , about  $5.75 \times 10^7$ , or about  $8 \times 10^7$  viable CAR-expressing cells.

In some embodiments, the dose calculation is based on the number of BCMA-CAR+ viable T-cells (e.g., single-positive BCMA CAR cells plus double-positive BCMA+/CD19+ CAR cells), measured by flow cytometry on day 4 (96h post-transduction (day 3 (72h) post-harvest), as described herein. In some embodiments, a dose of viable CAR-expressing cells (for example a BCMA/CD19 dual CART cellular product) comprises about  $5 \times 10^6$  to about  $2 \times 10^7$  CAR-positive viable cells (e.g., BCMA CAR+ T cells).

In some embodiments, a dose of viable CAR-expressing cells (for example, viable CD19, BCMA, CD20, or CD22 CAR-expressing cells) or a pharmaceutical composition comprising said cells is administered to the subject in one or more (e.g., 2, 3, 4, or more) doses. In some embodiments, the cells or pharmaceutical composition is administered to the subject in two doses. In some embodiments, the one or more doses comprises a first dose and a second dose, wherein the number of CAR-positive viable cells (e.g., BCMA CAR+ T cells) in the first dose is greater than, equal to, or less than the number of CAR-positive viable cells (e.g., BCMA CAR+ T cells) in the second dose.

In some embodiments, the one or more doses comprise a first dose and a second dose, wherein:

- (a) the first dose comprises about  $1 \times 10^6$  to about  $1 \times 10^7$  (e.g., about  $2 \times 10^6$  to about  $8 \times 10^6$ , about  $4 \times 10^6$  to about  $6 \times 10^6$ , about  $1 \times 10^6$  to about  $5 \times 10^6$ , about  $5 \times 10^6$  to about  $1 \times 10^7$ , about  $1 \times 10^6$  to about  $3 \times 10^6$ , about  $2 \times 10^6$  to about  $4 \times 10^6$ , about  $3 \times 10^6$  to about  $5 \times 10^6$ , about  $4 \times 10^6$  to about  $6 \times 10^6$ , about  $5 \times 10^6$  to about  $7 \times 10^6$ , about  $6 \times 10^6$  to about  $8 \times 10^6$ , about  $7 \times 10^6$  to about  $9 \times 10^6$ , about  $8 \times 10^6$  to about  $1 \times 10^7$ , about  $1 \times 10^6$ , about  $2 \times 10^6$ , about  $3 \times 10^6$ , about  $4 \times 10^6$ , about  $5 \times 10^6$ , about  $6 \times 10^6$ , about  $7 \times 10^6$ , about  $8 \times 10^6$ , about  $9 \times 10^6$ , or about  $1 \times 10^7$ ) viable CAR-positive cells (e.g., BCMA CAR+ T cells);
- (b) the second dose comprises about  $1 \times 10^7$  to about  $1 \times 10^8$  (e.g., about  $2 \times 10^7$  to about  $8 \times 10^7$ , about  $4 \times 10^7$  to about  $6 \times 10^7$ , about  $1 \times 10^7$  to about  $5 \times 10^7$ , about  $5 \times 10^7$  to about  $1 \times 10^8$ , about  $1 \times 10^7$  to about  $3 \times 10^7$ , about  $2 \times 10^7$  to about  $4 \times 10^7$ , about  $3 \times 10^7$  to about  $5 \times 10^7$ , about  $4 \times 10^7$  to about  $6 \times 10^7$ , about  $5 \times 10^7$  to about  $7 \times 10^7$ , about  $6 \times 10^7$  to about  $8 \times 10^7$ , about  $7 \times 10^7$  to about  $9 \times 10^7$ , about  $8 \times 10^7$  to about  $1 \times 10^8$ , about  $1 \times 10^7$ , about  $2 \times 10^7$ , about  $3 \times 10^7$ , about  $4 \times 10^7$ , about  $5 \times 10^7$ , about  $6 \times 10^7$ , about  $7 \times 10^7$ , about  $8 \times 10^7$ , about  $9 \times 10^7$ , or about  $1 \times 10^8$ ) CAR-positive viable cells (e.g., BCMA CAR+ T cells);
- (c) the number of CAR-positive viable cells (e.g., BCMA CAR+ T cells) in the first dose is no more than  $1/X$ , wherein X is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100, of the number of CAR-positive viable cells (e.g., BCMA CAR+ T cells) in the second dose; and/or
- (d) the number of CAR-positive viable cells (e.g., BCMA CAR+ T cells) in the first dose is between about 1% and 100% (e.g., between about 10% and about 90%, between about 20% and about 80%, between about 30% and about 70%, between about 40% and about 60%, between about 50% and about 90%, between about 10% and about 30%, between about 20% and about 40%, between about 30% and about 50%, between about 50% and about 70%, between about 60% and about 80%, or between about 70% and about 90%) of the number of CAR-positive viable cells (e.g., BCMA CAR+ T cells) in the second dose.

In some embodiments, the first dose comprises about  $5 \times 10^6$  viable CAR-positive cells (e.g., BCMA CAR+ T cells). In some embodiments, the second dose comprises about  $1 \times 10^7$  or about  $2 \times 10^7$  viable CAR-positive cells (e.g., BCMA CAR+ T cells).

In some embodiments, the dose of CAR-positive cells may be increased from the starting dose at a subsequent administration. For example, patient may receive a starting dose of about  $1 \times 10^6$  to about  $1 \times 10^7$  (e.g., about  $5 \times 10^6$ ) viable CAR-positive cells and may receive a second dose of about  $1 \times 10^7$  to about  $1 \times 10^8$  (e.g., about  $1 \times 10^7$  or about  $2 \times 10^7$ ) CAR-positive viable cells (e.g., BCMA CAR+ T cells).

#### Patient Selection

In some embodiments of any of the methods of treating a subject, or composition for use disclosed herein, the subject has a cancer, for example, a hematological cancer. In some embodiments, the cancer is chosen from lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), multiple myeloma, acute lymphoid leukemia (ALL), Hodgkin lymphoma, B-cell acute lymphoid leukemia (BALL), T-cell acute lymphoid leukemia (TALL), small lymphocytic leu-

kemia (SLL), B cell prolymphocytic leukemia, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, diffuse large B cell lymphoma (DLBCL), DLBCL associated with chronic inflammation, chronic myeloid leukemia, myeloproliferative neoplasms, follicular lymphoma, pediatric follicular lymphoma, hairy cell leukemia, small cell- or a large cell-follicular lymphoma, malignant lymphoproliferative conditions, MALT lymphoma (extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue), Marginal zone lymphoma, myelodysplasia, myelodysplastic syndrome, non-Hodgkin lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenstrom macroglobulinemia, splenic marginal zone lymphoma, splenic lymphoma/leukemia, splenic diffuse red pulp small B-cell lymphoma, hairy cell leukemia-variant, lymphoplasmacytic lymphoma, a heavy chain disease, plasma cell myeloma, solitary plasmacytoma of bone, extraosseous plasmacytoma, nodal marginal zone lymphoma, pediatric nodal marginal zone lymphoma, primary cutaneous follicle center lymphoma, lymphomatoid granulomatosis, primary mediastinal (thymic) large B-cell lymphoma, intravascular large B-cell lymphoma, ALK+ large B-cell lymphoma, large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease, primary effusion lymphoma, B-cell lymphoma, acute myeloid leukemia (AML), or unclassifiable lymphoma. In some embodiments, the cancer is a relapsed and/or refractory cancer.

In some embodiments of any of the methods of treating a subject, or composition for use disclosed herein, the subject has CLL or SLL. In some embodiments, the subject having CLL or SLL has previously been administered a BTK inhibitor therapy, for example, ibrutinib, for least 1-12 months, for example, 6 months. In some embodiments, the BTK inhibitor therapy, for example, ibrutinib therapy, is a second line therapy. In some embodiments, the subject had a partial response, or had stable disease in response to the BTK inhibitor therapy. In some embodiments, the subject did not respond to the BTK inhibitor therapy. In some embodiments, the subject developed resistance, for example, developed ibrutinib resistance mutations. In some embodiments, the ibrutinib resistance mutations comprise a mutation in the gene encoding BTK and/or the gene encoding PLCg2. In some embodiments, the subject is an adult, for example, at least 18 years of age.

In some embodiments of any of the methods of treating a subject, or composition for use disclosed herein, the subject has DLBCL, for example, relapsed and/or refractory DLBCL. In some embodiments, the subject having DLBCL, for example, relapsed and/or refractory DLBCL, has previously been administered at least 2 lines of chemotherapy, for example, an anti-CD20 therapy and/or an anthracycline-based chemotherapy. In some embodiments, the subject has previously received stem cell therapy, for example, autologous stem cell therapy, and has not responded to said stem cell therapy. In some embodiments, the subject is not eligible for stem cell therapy, for example, autologous stem cell therapy. In some embodiments, the subject is an adult, for example, at least 18 years of age.

#### Therapeutic Application

#### BCMA Associated Diseases and/or Disorders

In one aspect, the invention provides methods for treating a disease associated with BCMA expression. In one aspect, the invention provides methods for treating a disease wherein part of the tumor is negative for BCMA and part of the tumor is positive for BCMA. For example, the CAR of the invention is useful for treating subjects that have undergone treatment for a disease associated with elevated expres-

sion of BCMA, wherein the subject that has undergone treatment for elevated levels of BCMA exhibits a disease associated with elevated levels of BCMA. In embodiments, the CAR of the invention is useful for treating subjects that have undergone treatment for a disease associated with expression of BCMA, wherein the subject that has undergone treatment related to expression of BCMA exhibits a disease associated with expression of BCMA.

In one embodiment, the invention provides methods for 10 treating a disease wherein BCMA is expressed on both normal cells and cancers cells, but is expressed at lower levels on normal cells. In one embodiment, the method further comprises selecting a CAR that binds of the invention with an affinity that allows the BCMA CAR to bind and kill the cancer cells expressing BCMA but less than 30%, 15 25%, 20%, 15%, 10%, 5% or less of the normal cells expressing BCMA are killed, e.g., as determined by an assay described herein. For example, a killing assay such as flow cytometry based on Cr51 CTL can be used. In one embodiment, the BCMA CAR has an antigen binding domain that has a binding affinity KD of  $10^{-4}$  M to  $10^{-8}$  M, e.g.,  $10^{-5}$  M to  $10^{-7}$  M, e.g.,  $10^{-6}$  M or  $10^{-7}$  M, for the target antigen. In one embodiment, the BCMA antigen binding domain has a binding affinity that is at least five-fold, 10-fold, 20-fold, 25 30-fold, 50-fold, 100-fold or 1,000-fold less than a reference antibody, e.g., an antibody described herein.

In one aspect, the invention pertains to a vector comprising 30 BCMA CAR operably linked to promoter for expression in mammalian immune effector cells, e.g., T cells or NK cells. In one aspect, the invention provides a recombinant immune effector cell, e.g., T cell or NK cell, expressing the BCMA CAR for use in treating BCMA-expressing tumors, wherein the recombinant immune effector cell (e.g., T cell or NK cell) expressing the BCMA CAR is termed a BCMA 35 CAR-expressing cell (e.g., BCMA CART or BCMA CAR-expressing NK cell). In one aspect, the BCMA CAR-expressing cell (e.g., BCMA CART or BCMA CAR-expressing NK cell) of the invention is capable of contacting a tumor cell with at least one BCMA CAR of the invention expressed on its surface such that the BCMA CAR-expressing cell (e.g., BCMA CART or BCMA CAR-expressing NK cell) targets the tumor cell and growth of the tumor is inhibited.

In one aspect, the invention pertains to a method of 45 inhibiting growth of a BCMA-expressing tumor cell, comprising contacting the tumor cell with a BCMA CAR-expressing cell (e.g., BCMA CART or BCMA CAR-expressing NK cell) of the present invention such that the BCMA CAR-expressing cell (e.g., BCMA CART or BCMA 50 CAR-expressing NK cell) is activated in response to the antigen and targets the cancer cell, wherein the growth of the tumor is inhibited.

In one aspect, the invention pertains to a method of 55 treating cancer in a subject. The method comprises administering to the subject a BCMA CAR-expressing cell (e.g., BCMA CART or BCMA CAR-expressing NK cell) of the present invention such that the cancer is treated in the subject. An example of a cancer that is treatable by the BCMA CAR-expressing cell (e.g., BCMA CART or BCMA 60 CAR-expressing NK cell) of the invention is a cancer associated with expression of BCMA.

The invention includes a type of cellular therapy where 65 immune effector cells (e.g., T cells or NK cells) are genetically modified to express a chimeric antigen receptor (CAR) and the BCMA CAR-expressing cell (e.g., BCMA CART or BCMA CAR-expressing NK cell) is infused to a recipient in need thereof. The infused cell is able to kill tumor cells in the

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recipient. Unlike antibody therapies, CAR-modified cells, e.g., T cells or NK cells, are able to replicate in vivo resulting in long-term persistence that can lead to sustained tumor control. In various aspects, the cells (e.g., T cells or NK cells) administered to the patient, or their progeny, persist in the patient for at least four months, five months, six months, seven months, eight months, nine months, ten months, eleven months, twelve months, thirteen months, fourteen months, fifteen months, sixteen months, seventeen months, eighteen months, nineteen months, twenty months, twenty-one months, twenty-two months, twenty-three months, two years, three years, four years, or five years after administration of the cell (e.g., T cell or NK cell) to the patient.

The invention also includes a type of cellular therapy where immune effector cells (e.g., T cells or NK cells) are modified, e.g., by in vitro transcribed RNA, to transiently express a chimeric antigen receptor (CAR) and the immune effector cell (e.g., T cell or NK cell) is infused to a recipient in need thereof. The infused cell is able to kill tumor cells in the recipient. Thus, in various aspects, the immune effector cells (e.g., T cells or NK cells) administered to the patient, is present for less than one month, e.g., three weeks, two weeks, one week, after administration of the immune effector cell (e.g., T cell or NK cell) to the patient.

Without wishing to be bound by theory, the anti-tumor immunity response elicited by the CAR-modified immune effector cells (e.g., T cells or NK cells) may be an active or a passive immune response, or alternatively may be due to a direct vs indirect immune response. In one aspect, the CAR transduced immune effector cells (e.g., T cells or NK cells) exhibit specific proinflammatory cytokine secretion and potent cytolytic activity in response to human cancer cells expressing the BCMA, resist soluble BCMA inhibition, mediate bystander killing and mediate regression of an established human tumor. For example, antigen-less tumor cells within a heterogeneous field of BCMA-expressing tumor may be susceptible to indirect destruction by BCMA-directed immune effector cells (e.g., T cells or NK cells) that has previously reacted against adjacent antigen-positive cancer cells.

In one aspect, the fully-human CAR-modified immune effector cells (e.g., T cells or NK cells) of the invention may be a type of vaccine for ex vivo immunization and/or in vivo therapy in a mammal. In one aspect, the mammal is a human.

With respect to ex vivo immunization, at least one of the following occurs in vitro prior to administering the cell into a mammal: i) expansion of the cells, ii) introducing a nucleic acid encoding a CAR to the cells or iii) cryopreservation of the cells.

Ex vivo procedures are well known in the art and are discussed more fully below. Briefly, 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 cell can be administered to a mammalian recipient to provide a therapeutic benefit. The mammalian recipient may be a human and 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 procedure for ex vivo expansion of hematopoietic stem and progenitor cells is described in U.S. Pat. No. 5,199,942, incorporated herein by reference, can be applied to the cells of the present invention. Other suitable methods are known in the art, therefore the present invention is not limited to any particular method of ex vivo expansion of the cells. Briefly, ex vivo culture and expansion of T cells

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comprises: (1) collecting CD34+ hematopoietic stem and progenitor cells from a mammal from peripheral blood harvest or bone marrow explants; and (2) expanding such cells ex vivo. In addition to the cellular growth factors described in U.S. Pat. No. 5,199,942, other factors such as flt3-L, IL-1, IL-3 and c-kit ligand, can be used for culturing and expansion of the cells.

In addition to using a cell-based vaccine in terms of ex vivo immunization, the present invention also provides compositions and methods for in vivo immunization to elicit an immune response directed against an antigen in a patient.

Generally, the cells activated and expanded as described herein may be utilized in the treatment and prevention of diseases that arise in individuals who are immunocompromised. For example, the CAR-modified immune effector cells (e.g., T cells or NK cells) of the invention are used in the treatment of diseases, disorders and conditions associated with expression of BCMA. In some aspects, the cells of the invention are used in the treatment of patients at risk for developing diseases, disorders and conditions associated with expression of BCMA. Thus, the present invention provides methods for the treatment or prevention of diseases, disorders and conditions associated with expression of BCMA comprising administering to a subject in need thereof, a therapeutically effective amount of the CAR-modified immune effector cells (e.g., T cells or NK cells) of the invention.

In one aspect the CAR-expressing cells (e.g., CART cells or CAR-expressing NK cells) of the inventions may be used to treat a proliferative disease such as a cancer or malignancy or is a precancerous condition such as a myelodysplasia, a myelodysplastic syndrome or a preleukemia. In one aspect, the cancer is a hematological cancer. Hematological cancer conditions are the types of cancer such as leukemia and malignant lymphoproliferative conditions that affect blood, bone marrow and the lymphatic system. In one aspect, the hematological cancer is a leukemia or a hematological. An example of a disease or disorder associated with BCMA is multiple myeloma (also known as MM) (See Claudio et al., Blood. 2002, 100(6):2175-86; and Novak et al., Blood. 2004, 103(2):689-94). Multiple myeloma, also known as plasma cell myeloma or Kahler's disease, is a cancer characterized by an accumulation of abnormal or malignant plasma B-cells in the bone marrow. Frequently, the cancer cells invade adjacent bone, destroying skeletal structures and resulting in bone pain and fractures. Most cases of myeloma also features the production of a paraprotein (also known as M proteins or myeloma proteins), which is an abnormal immunoglobulin produced in excess by the clonal proliferation of the malignant plasma cells. Blood serum paraprotein levels of more than 30 g/L is diagnostic of multiple myeloma, according to the diagnostic criteria of the International Myeloma Working Group (IMWG) (See Kyle et al. (2009), Leukemia. 23:3-9). Other symptoms or signs of multiple myeloma include reduced kidney function or renal failure, bone lesions, anemia, hypercalcemia, and neurological symptoms.

Criteria for distinguishing multiple myeloma from other plasma cell proliferative disorders have been established by the International Myeloma Working Group (See Kyle et al. (2009), Leukemia. 23:3-9). All three of the following criteria must be met:

Clonal bone marrow plasma cells ≥10%

Present of serum and/or urinary monoclonal protein (except in patients with true non-secretory multiple myeloma)

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Evidence of end-organ damage attributable to the underlying plasma cell proliferative disorder, specifically:

Hypercalcemia: serum calcium >11.5 mg/100 ml

Renal insufficiency: serum creatinine >1.73 mmol/l

Anemia: normochromic, normocytic with a hemoglobin value of >2 g/100 ml below the lower limit of normal, or a hemoglobin value <10 g/100 ml

Bone lesions: lytic lesions, severe osteopenia, or pathologic fractures.

Other plasma cell proliferative disorders that can be treated by the compositions and methods described herein include, but are not limited to, asymptomatic myeloma (smoldering multiple myeloma or indolent myeloma), monoclonal gammopathy of undetermined significance (MGUS), Waldenstrom's macroglobulinemia, plasmacytomas (e.g., plasma cell dyscrasia, solitary myeloma, solitary plasmacytoma, extramedullary plasmacytoma, and multiple plasmacytoma), systemic amyloid light chain amyloidosis, and POEMS syndrome (also known as Crow-Fukase syndrome, Takatsuki disease, and PEP syndrome).

Two staging systems are used in the staging of multiple myeloma: the International Staging System (ISS) (See Greipp et al. (2005), J. Clin. Oncol. 23 (15):3412-3420) and the Durie-Salmon Staging system (DSS) (See Durie et al. (1975), Cancer 36 (3): 842-854).

A third staging system for multiple myeloma is referred to as Revised International Staging System (R-ISS) (see Palumbo A, Avet-Loiseau H, Oliva S, et al. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 2015; 33:2863-9, herein incorporated by reference in its entirety). R-ISS stage I includes ISS stage I (serum 02-microglobulin level <3.5 mg/L and serum albumin level  $\geq 3.5$  g/dL), no high-risk CA [del(17p) and/or t(4;14) and/or t(14;16)], and normal LDH level (less than the upper limit of normal range). R-ISS stage III includes ISS stage III (serum 02-microglobulin level >5.5 mg/L) and high-risk CA or high LDH level. R-ISS stage II includes all the other possible combinations.

The response of patients can be determined based on IMWG 2016 criteria, as disclosed in Kumar S, Paiva B, Anderson K C, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. The Lancet Oncology; 17(8):e328-e346, herein incorporated by reference in its entirety.

Standard treatment for multiple myeloma and associated diseases includes chemotherapy, stem cell transplant (autologous or allogeneic), radiation therapy, and other drug therapies. Frequently used anti-myeloma drugs include alkylating agents (e.g., bendamustine, cyclophosphamide and melphalan), proteasome inhibitors (e.g., bortezomib), corticosteroids (e.g., dexamethasone and prednisone), and immunomodulators (e.g., thalidomide and lenalidomide or Revlimid®), or any combination thereof.

Biphosphonate drugs are also frequently administered in combination with the standard anti-MM treatments to prevent bone loss. Patients older than 65-70 years of age are unlikely candidates for stem cell transplant. In some cases, double-autologous stem cell transplants are options for patients less than 60 years of age with suboptimal response to the first transplant. The compositions and methods of the present invention may be administered in combination with any of the currently prescribed treatments for multiple myeloma.

Another example of a disease or disorder associated with BCMA is Hodgkin's lymphoma and non-Hodgkin's lym-

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phoma (See Chiu et al., Blood. 2007, 109(2):729-39; He et al., J Immunol. 2004, 172(5):3268-79).

Hodgkin's lymphoma (HL), also known as Hodgkin's disease, is a cancer of the lymphatic system that originates from white blood cells, or lymphocytes. The abnormal cells that comprise the lymphoma are called Reed-Sternberg cells. In Hodgkin's lymphoma, the cancer spreads from one lymph node group to another. Hodgkin's lymphoma can be subclassified into four pathologic subtypes based upon Reed-Sternberg cell morphology and the cell composition around the Reed-Sternberg cells (as determined through lymph node biopsy): nodular sclerosing HL, mixed-cellularity subtype, lymphocyte-rich or lymphocytic predominance, lymphocyte depleted. Some Hodgkin's lymphoma can also be nodular lymphocyte predominant Hodgkin's lymphoma, or can be unspecified. Symptoms and signs of Hodgkin's lymphoma include painless swelling in the lymph nodes in the neck, armpits, or groin, fever, night sweats, weight loss, fatigue, itching, or abdominal pain.

Non-Hodgkin's lymphoma (NHL) comprises a diverse group of blood cancers that include any kind of lymphoma other than Hodgkin's lymphoma. Subtypes of non-Hodgkin's lymphoma are classified primarily by cell morphology, chromosomal aberrations, and surface markers. NHL subtypes (or NHL-associated cancers) include B cell lymphomas such as, but not limited to, Burkitt's lymphoma, B-cell chronic lymphocytic leukemia (B-CLL), B-cell prolymphocytic leukemia (B-PLL), chronic lymphocytic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL) (e.g., intravascular large B-cell lymphoma and primary mediastinal B-cell lymphoma), follicular lymphoma (e.g., follicle center lymphoma, follicular small cleaved cell), hairy cell leukemia, high grade B-cell lymphoma (Burkitt's like), lymphoplasmacytic lymphoma (Waldenstrom's macroglobulinemia), mantle cell lymphoma, marginal zone B-cell lymphomas (e.g., extranodal marginal zone B-cell lymphoma or mucosa-associated lymphoid tissue (MALT) lymphoma, nodal marginal zone B-cell lymphoma, and splenic marginal zone B-cell lymphoma), plasmacytoma/myeloma, precursor B-lymphoblastic leukemia/lymphoma (PB-LBL/L), primary central nervous system (CNS) lymphoma, primary intraocular lymphoma, small lymphocytic lymphoma (SLL); and T cell lymphomas, such as, but not limited to, anaplastic large cell lymphoma (ALCL), adult T-cell lymphoma/leukemia (e.g., smoldering, chronic, acute and lymphomatous), angiocentric lymphoma, angioimmunoblastic T-cell lymphoma, cutaneous T-cell lymphomas (e.g., mycosis fungoïdes, Sézary syndrome, etc.), extranodal natural killer/T-cell lymphoma (nasal-type), enteropathy type intestinal T-cell lymphoma, large granular lymphocyte leukemia, precursor T-lymphoblastic lymphoma/leukemia (T-LBL/L), T-cell chronic lymphocytic leukemia/prolymphocytic leukemia (T-CLL/PLL), and unspecified peripheral T-cell lymphoma. Symptoms and signs of Hodgkin's lymphoma include painless swelling in the lymph nodes in the neck, armpits, or groin, fever, night sweats, weight loss, fatigue, itching, abdominal pain, coughing, or chest pain.

The staging is the same for both Hodgkin's and non-Hodgkin's lymphoma, and refers to the extent of spread of the cancer cells within the body. In stage I, the lymphoma cells are in one lymph node group. In stage II, lymphoma cells are present in at least two lymph node groups, but both groups are on the same side of the diaphragm, or in one part of a tissue or organ and the lymph nodes near that organ on the same side of the diaphragm. In stage III, lymphoma cells are in lymph nodes on both sides of the diaphragm, or in one part of a tissue or organ near these lymph node groups or in

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the spleen. In stage IV, lymphoma cells are found in several parts of at least one organ or tissue, or lymphoma cells are in an organ and in lymph nodes on the other side of the diaphragm. In addition to the Roman numeral staging designation, the stages of can also be described by letters A, B, E, and S, wherein A refers to patients without symptoms, B refers to patients with symptoms, E refers to patients in which lymphoma is found in tissues outside the lymph system, and S refers to patients in which lymphoma is found in the spleen.

Hodgkin's lymphoma is commonly treated with radiation therapy, chemotherapy, or hematopoietic stem cell transplantation. The most common therapy for non-Hodgkin's lymphoma is R-CHOP, which consists of four different chemotherapies (cyclophosphamide, doxorubicin, vincristine, and prednisone) and rituximab (Rituxan®). Other therapies commonly used to treat NHL include other chemotherapeutic agents, radiation therapy, stem cell transplantation (autologous or allogeneic bone marrow transplantation), or biological therapy, such as immunotherapy. Other examples of biological therapeutic agents include, but are not limited to, rituximab (Rituxan®), tositumomab (Bexxar®), epratuzumab (LymphoCide®), and alemtuzumab (MabCampath®). The compositions and methods of the present invention may be administered in combination with any of the currently prescribed treatments for Hodgkin's lymphoma or non-Hodgkin's lymphoma.

BCMA expression has also been associated Waldenstrom's macroglobulinemia (WM), also known as lymphoplasmacytic lymphoma (LPL). (See Elsawa et al., Blood. 2006, 107(7):2882-8). Waldenstrom's macroglobulinemia was previously considered to be related to multiple myeloma, but has more recently been classified as a subtype of non-Hodgkin's lymphoma. WM is characterized by uncontrolled B-cell lymphocyte proliferation, resulting in anemia and production of excess amounts of paraprotein, or immunoglobulin M (IgM), which thickens the blood and results in hyperviscosity syndrome. Other symptoms or signs of WM include fever, night sweats, fatigue, anemia, weight loss, lymphadenopathy or splenomegaly, blurred vision, dizziness, nose bleeds, bleeding gums, unusual bruises, renal impairment or failure, amyloidosis, or peripheral neuropathy.

Standard treatment for WM consists of chemotherapy, specifically with rituximab (Rituxan®). Other chemotherapeutic drugs can be used in combination, such as chlorambucil (Leukeran®), cyclophosphamide (Neosar®), fludarabine (Fludara®), cladribine (Leustatin®), vincristine, and/or thalidomide. Corticosteroids, such as prednisone, can also be administered in combination with the chemotherapy. Plasmapheresis, or plasma exchange, is commonly used throughout treatment of the patient to alleviate some symptoms by removing the paraprotein from the blood. In some cases, stem cell transplantation is an option for some patients.

Another example of a disease or disorder associated with BCMA is brain cancer. Specifically, expression of BCMA has been associated with astrocytoma or glioblastoma (See Deshayes et al, Oncogene. 2004, 23(17):3005-12; Pelekanou et al., PLoS One. 2013, 8(12):e83250). Astrocytomas are tumors that arise from astrocytes, which are a type of glial cell in the brain. Glioblastoma (also known as glioblastoma multiforme or GBM) is the most malignant form of astrocytoma, and is considered the most advanced stage of brain cancer (stage IV). There are two variants of glioblastoma: giant cell glioblastoma and gliosarcoma. Other astrocytomas include juvenile pilocytic astrocytoma (JPA), fibrillary

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astrocytoma, pleomorphic xanthroastrocytoma (PXA), desembryoplastic neuroepithelial tumor (DNET), and anaplastic astrocytoma (AA).

Symptoms or signs associated with glioblastoma or astrocytoma include increased pressure in the brain, headaches, seizures, memory loss, changes in behavior, loss in movement or sensation on one side of the body, language dysfunction, cognitive impairments, visual impairment, nausea, vomiting, and weakness in the arms or legs.

10 Surgical removal of the tumor (or resection) is the standard treatment for removal of as much of the glioma as possible without damaging or with minimal damage to the normal, surrounding brain. Radiation therapy and/or chemotherapy are often used after surgery to suppress and slow 15 recurrent disease from any remaining cancer cells or satellite lesions. Radiation therapy includes whole brain radiotherapy (conventional external beam radiation), targeted three-dimensional conformal radiotherapy, and targeted radionuclides. Chemotherapeutic agents commonly used to treat 20 glioblastoma include temozolamide, gefitinib or erlotinib, and cisplatin. Angiogenesis inhibitors, such as Bevacizumab (Avastin®), are also commonly used in combination with chemotherapy and/or radiotherapy.

Supportive treatment is also frequently used to relieve 25 neurological symptoms and improve neurologic function, and is administered in combination any of the cancer therapies described herein. The primary supportive agents include anticonvulsants and corticosteroids. Thus, the compositions and methods of the present invention may be used in 30 combination with any of the standard or supportive treatments to treat a glioblastoma or astrocytoma.

Non-cancer related diseases and disorders associated with BCMA expression can also be treated by the compositions and methods disclosed herein. Examples of non-cancer 35 related diseases and disorders associated with BCMA expression include, but are not limited to: viral infections; e.g., HIV, fungal infections, e.g., *C. neoformans*; irritable bowel disease; ulcerative colitis, and disorders related to mucosal immunity.

40 The CAR-modified immune effector cells (e.g., T cells or NK cells) of the present invention may be administered either alone, or as a pharmaceutical composition in combination with diluents and/or with other components such as IL-2 or other cytokines or cell populations.

45 The present invention provides for compositions and methods for treating cancer. In one aspect, the cancer is a hematologic cancer including but is not limited to hematological cancer is a leukemia or a lymphoma. In one aspect, the CAR-expressing cells (e.g., CART cells or CAR-expressing NK cells) of the invention may be used to treat cancers and malignancies such as, but not limited to, e.g., acute leukemias including but not limited to, e.g., B-cell acute lymphoid leukemia ("BALL"), T-cell acute lymphoid leukemia ("TALL"), acute lymphoid leukemia (ALL); one 50 or more chronic leukemias including but not limited to, e.g., chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL); additional hematologic cancers or hematologic conditions including, but not limited to, e.g., B cell prolymphocytic leukemia, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, diffuse large B cell lymphoma, Follicular lymphoma, Hairy cell leukemia, small cell- or a large cell-follicular lymphoma, malignant lymphoproliferative conditions, MALT lymphoma, mantle cell lymphoma, Marginal zone lymphoma, multiple 55 myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin's lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenstrom macro-

globulinemia, and “preleukemia” which are a diverse collection of hematological conditions united by ineffective production (or dysplasia) of myeloid blood cells, and the like. Further a disease associated with BCMA expression includes, but not limited to, e.g., atypical and/or non-classical cancers, malignancies, precancerous conditions or proliferative diseases expressing BCMA.

In embodiments, a composition described herein can be used to treat a disease including but not limited to a plasma cell proliferative disorder, e.g., asymptomatic myeloma (smoldering multiple myeloma or indolent myeloma), monoclonal gammopathy of undetermined significance (MGUS), Waldenstrom's macroglobulinemia, plasmacytomas (e.g., plasma cell dyscrasia, solitary myeloma, solitary plasmacytoma, extramedullary plasmacytoma, and multiple plasmacytoma), systemic amyloid light chain amyloidosis, and POEMS syndrome (also known as Crow-Fukase syndrome, Takatsuki disease, and PEP syndrome).

In embodiments, a composition described herein can be used to treat a disease including but not limited to a cancer, e.g., a cancer described herein, e.g., a prostate cancer (e.g., castrate-resistant or therapy-resistant prostate cancer, or metastatic prostate cancer), pancreatic cancer, or lung cancer.

The present invention also provides methods for inhibiting the proliferation or reducing a BCMA-expressing cell population, the methods comprising contacting a population of cells comprising a BCMA-expressing cell with an anti-BCMA CAR-expressing cell (e.g., BCMA CART cell or BCMA CAR-expressing NK cell) of the invention that binds to the BCMA-expressing cell. In a specific aspect, the present invention provides methods for inhibiting the proliferation or reducing the population of cancer cells expressing BCMA, the methods comprising contacting the BCMA-expressing cancer cell population with an anti-BCMA CAR-expressing cell (e.g., BCMA CART cell or BCMA CAR-expressing NK cell) of the invention that binds to the BCMA-expressing cell. In one aspect, the present invention provides methods for inhibiting the proliferation or reducing the population of cancer cells expressing BCMA, the methods comprising contacting the BCMA-expressing cancer cell population with an anti-BCMA CAR-expressing cell (e.g., BCMA CART cell or BCMA CAR-expressing NK cell) of the invention that binds to the BCMA-expressing cell. In some aspects, the anti-BCMA CAR-expressing cell (e.g., BCMA CART cell or BCMA CAR-expressing NK cell) of the invention reduces the quantity, number, amount or percentage of cells and/or cancer cells by at least 25%, at least 30%, at least 40%, at least 50%, at least 65%, at least 75%, at least 85%, at least 95%, or at least 99% in a subject with or animal model for myeloid leukemia or another cancer associated with BCMA-expressing cells relative to a negative control. In one aspect, the subject is a human.

The present invention also provides methods for preventing, treating and/or managing a disease associated with BCMA-expressing cells (e.g., a hematologic cancer or atypical cancer expressing BCMA), the methods comprising administering to a subject in need an anti-BCMA CAR-expressing cell (e.g., BCMA CART cell or BCMA CAR-expressing NK cell) of the invention that binds to the BCMA-expressing cell. In one aspect, the subject is a human. Non-limiting examples of disorders associated with BCMA-expressing cells include viral or fungal infections, and disorders related to mucosal immunity.

The present invention also provides methods for preventing, treating and/or managing a disease associated with BCMA-expressing cells, the methods comprising adminis-

tering to a subject in need an anti-BCMA CAR-expressing cell (e.g., BCMA CART cell or BCMA CAR-expressing NK cell) of the invention that binds to the BCMA-expressing cell. In one aspect, the subject is a human.

5 The present invention provides methods for preventing relapse of cancer associated with BCMA-expressing cells, the methods comprising administering to a subject in need thereof an anti-BCMA CAR-expressing cell (e.g., BCMA CART cell or BCMA CAR-expressing NK cell) of the invention that binds to the BCMA-expressing cell. In one aspect, the methods comprise administering to the subject in need thereof an effective amount of an anti-BCMA CAR-expressing cell (e.g., BCMA CART cell or BCMA CAR-expressing NK cell) described herein that binds to the BCMA-expressing cell in combination with an effective amount of another therapy.

#### Combination Therapies

A CAR-expressing cell described herein may be used in combination with other known agents and therapies. A CAR-expressing cell described herein and the at least one additional therapeutic agent can be administered simultaneously, in the same or in separate compositions, or sequentially. For sequential administration, the CAR-expressing cell described herein can be administered first, and the additional agent can be administered second, or the order of administration can be reversed. The CAR therapy and/or other therapeutic agents, procedures or modalities can be administered during periods of active disorder, or during a period of remission or less active disease. The CAR therapy can be administered before the other treatment, concurrently with the treatment, post-treatment, or during remission of the disorder. When administered in combination, the CAR therapy and the additional agent (e.g., second or third agent), or all, can be administered in an amount or dose that is higher, lower or the same than the amount or dosage of each agent used individually, e.g., as a monotherapy. In some embodiments, the administered amount or dosage of the CAR therapy, the additional agent (e.g., second or third agent), or all, is lower (e.g., at least 20%, at least 30%, at least 40%, or at least 50%) than the amount or dosage of each agent used individually, e.g., as a monotherapy. In other embodiments, the amount or dosage of the CAR therapy, the additional agent (e.g., second or third agent), or all, that results in a desired effect (e.g., treatment of cancer) is lower (e.g., at least 20%, at least 30%, at least 40%, or at least 50% lower) than the amount or dosage of each agent used individually, e.g., as a monotherapy, required to achieve the same therapeutic effect. In further aspects, a CAR-expressing cell described herein may be used in a treatment regimen in combination with surgery, chemotherapy, radiation, immunosuppressive agents. Exemplary agents and therapies that can be used in combination with a CAR-expressing cell described herein are disclosed on pages 266-313 of WO2016164731, herein incorporated by reference in its entirety.

#### Biomarkers for Evaluating CAR-Effectiveness

In some embodiments, disclosed herein is a method of evaluating or monitoring the effectiveness of a CAR-expressing cell therapy (for example, a CD19 or BCMA CAR therapy), in a subject (for example, a subject having a cancer, for example, a hematological cancer). The method includes acquiring a value of effectiveness to the CAR therapy, wherein said value is indicative of the effectiveness or suitability of the CAR-expressing cell therapy.

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In embodiments, the value of effectiveness to the CAR therapy in a subject having CLL or SLL, comprises a measure of one, two, three, or all of the following parameters:

- (i) a mutation in a gene encoding BTK in a sample (for example, an apheresis sample or a manufactured CAR-expressing cell product sample);
- (ii) a mutation in a gene encoding PLCg2 in a sample (for example, an apheresis sample or a manufactured CAR-expressing cell product sample);
- (iii) minimal residual disease, for example, as evaluated by the level and/or activity of CD8, CD4, CD3, CD5, CD19, CD20, CD22, CD43, CD79b, CD27, CD45RO, CD45RA, CCR7, CD95, Lag3, PD-1, Tim-3, and/or CD81; or as evaluated by immunoglobulin deep sequencing; in a sample (for example, an apheresis sample or tumor sample from the subject); or
- (iv) the level or activity of one, two, three, four, five, six, seven, eight, nine, ten or all of the cytokines chosen from IFN-g, IL-2, IL-4, IL-6, IL-8, IL-10, IL-15, TNF- $\alpha$ , IP-10, MCP1, MIP1a, in a sample, for example, an apheresis sample from the subject.

In embodiments, the value of effectiveness to the CAR therapy in a subject having DLBCL, for example, relapsed and/or refractory DLBCL, comprises a measure of one or both of the following parameters:

- (i) minimal residual disease, for example, as evaluated by the level and/or activity of CD8, CD4, CAR19, CD3, CD27, CD45RO, CD45RA, CCR7, CD95, Lag3, PD-1, and/or Tim-3; or as evaluated by immunoglobulin deep sequencing; in a sample (for example, an apheresis sample or tumor sample from the subject); or
- (ii) the level or activity of one, two, three, four, five, six, seven, eight, nine, ten or all of the cytokines chosen from IFN-g, IL-2, IL-4, IL-6, IL-8, IL-10, IL-15, TNF-a, IP-10, MCP1, MIP1a, in a sample (for example, an apheresis sample from the subject).

In other embodiments, the value of effectiveness to the CAR therapy, further comprises a measure of one, two, three, four, five, six or more (all) of the following parameters:

- (i) the level or activity of one, two, three, or more (for example, all) of resting  $T_{EFF}$  cells, resting  $T_{REG}$  cells, younger T cells (for example, naïve T cells (for example, naïve CD4 or CD8 T cells, naïve gamma/delta T cells), or stem memory T cells (for example, stem memory CD4 or CD8 T cells, or stem memory gamma/delta T cells), or early memory T cells, or a combination thereof, in a sample (for example, an apheresis sample or a manufactured CAR-expressing cell product sample);
- (ii) the level or activity of one, two, three, or more (for example, all) of activated  $T_{EFF}$  cells, activated  $T_{REG}$  cells, older T cells (for example, older CD4 or CD8 cells), or late memory T cells, or a combination thereof, in a sample (for example, an apheresis sample or a manufactured CAR-expressing cell product sample);
- (iii) the level or activity of an immune cell exhaustion marker, for example, one, two or more immune checkpoint inhibitors (for example, PD-1, PD-L1, TIM-3, TIGIT and/or LAG-3) in a sample (for example, an apheresis sample or a manufactured CAR-expressing cell product sample). In some embodiments, an immune cell has an exhausted phenotype, for example, co-expresses at least two exhaustion markers, for example, co-expresses PD-1 and TIM-3. In other embodiments, an immune cell has an exhausted phe-

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notype, for example, co-expresses at least two exhaustion markers, for example, co-expresses PD-1 and LAG-3;

- (iv) the level or activity of CD27 and/or CD45RO- (for example, CD27+CD45RO-) immune effector cells, for example, in a CD4+ or a CD8+ T cell population, in a sample (for example, an apheresis sample or a manufactured CAR-expressing cell product sample);
- (v) the level or activity of one, two, three, four, five, six, seven, eight, nine, ten, eleven or all of the biomarkers chosen from CCL20, IL-17a, IL-6, PD-1, PD-L1, LAG-3, TIM-3, CD57, CD27, CD122, CD62L, KLRG1;
- (vi) a cytokine level or activity (for example, quality of cytokine repertoire) in a CAR-expressing cell product sample, for example, CLL-1-expressing cell product sample; or
- (vii) a transduction efficiency of a CAR-expressing cell in a manufactured CAR-expressing cell product sample.

In some embodiments of any of the methods disclosed herein, the CAR-expressing cell therapy comprises a plurality (for example, a population) of CAR-expressing immune effector cells, for example, a plurality (for example, a population) of T cells or NK cells, or a combination thereof. In some embodiments, the CAR-expressing cell therapy is a CD19 CAR therapy.

In some embodiments of any of the methods disclosed herein, the measure of one or more of the parameters disclosed herein is obtained from an apheresis sample acquired from the subject. The apheresis sample can be evaluated prior to infusion or re-infusion.

In some embodiments of any of the methods disclosed herein, the measure of one or more of the parameters disclosed herein is obtained from a tumor sample acquired from the subject.

In some embodiments of any of the methods disclosed herein, the measure of one or more of the parameters disclosed herein is obtained from a manufactured CAR-expressing cell product sample, for example, CD19 CAR-expressing cell product sample. The manufactured CAR-expressing cell product can be evaluated prior to infusion or re-infusion.

In some embodiments of any of the methods disclosed herein, the subject is evaluated prior to receiving, during, or after receiving, the CAR-expressing cell therapy.

In some embodiments of any of the methods disclosed herein, the measure of one or more of the parameters disclosed herein evaluates a profile for one or more of gene expression, flow cytometry or protein expression.

In some embodiments of any of the methods disclosed herein, the method further comprises identifying the subject as a responder, a non-responder, a relapser or a non-relapser, based on a measure of one or more of the parameters disclosed herein.

In some embodiments of any of the methods disclosed herein, a responder, for example, complete responder has, or is identified as having, a greater, for example, a statistically significant greater, percentage of CD8+ T cells compared to a reference value, for example, a non-responder percentage of CD8+ T cells.

In some embodiments of any of the methods disclosed herein, a responder, for example, complete responder has, or is identified as having, a greater percentage of CD27+ CD45RO- immune effector cells, for example, in the CD8+ population, compared to a reference value, for example, a non-responder number of CD27+CD45RO- immune effector cells.

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In some embodiments of any of the methods disclosed herein, a responder, for example, complete responder or a partial responder has, or is identified as having, a greater, for example, a statistically significant greater, percentage of CD4+ T cells compared to a reference value, for example, a non-responder percentage of CD4+ T cells.

In some embodiments of any of the methods disclosed herein, a responder, for example, complete responder has, or is identified as having, a greater percentage of one, two, three, or more (for example, all) of resting  $T_{EFF}$  cells, resting  $T_{REG}$  cells, younger T cells, or early memory T cells, or a combination thereof, compared to a reference value, for example, a non-responder number of resting  $T_{EFF}$  cells, resting  $T_{REG}$  cells, younger T cells, or early memory T cells.

In some embodiments of any of the methods disclosed herein, a non-responder has, or is identified as having, a greater percentage of one, two, three, or more (for example, all) of activated  $T_{EFF}$  cells, activated  $T_{REG}$  cells, older T cells (for example, older CD4 or CD8 cells), or late memory T cells, or a combination thereof, compared to a reference value, for example, a responder number of activated  $T_{EFF}$  cells, activated  $T_{REG}$  cells, older T cells (for example, older CD4 or CD8 cells), or late memory T cells.

In some embodiments of any of the methods disclosed herein, a non-responder has, or is identified as having, a greater percentage of an immune cell exhaustion marker, for example, one, two or more immune checkpoint inhibitors (for example, PD-1, PD-L1, TIM-3, TIGIT, and/or LAG-3). In some embodiments, a non-responder has, or is identified as having, a greater percentage of PD-1, PD-L1, or LAG-3 expressing immune effector cells (for example, CD4+ T cells and/or CD8+ T cells) (for example, CAR-expressing CD4+ cells and/or CD8+ T cells) compared to the percentage of PD-1 or LAG-3 expressing immune effector cells from a responder.

In some embodiments, a non-responder has, or is identified as having, a greater percentage of immune cells having an exhausted phenotype, for example, immune cells that co-express at least two exhaustion markers, for example, co-expresses PD-1, PD-L1 and/or TIM-3. In other embodiments, a non-responder has, or is identified as having, a greater percentage of immune cells having an exhausted phenotype, for example, immune cells that co-express at least two exhaustion markers, for example, co-expresses PD-1 and LAG-3.

In some embodiments of any of the methods disclosed herein, a non-responder has, or is identified as having, a greater percentage of PD-1/PD-L1+/LAG-3+ cells in the CAR-expressing cell population (for example, a CLL-1 CAR+ cell population) compared to a responder (for example, a complete responder) to the CAR-expressing cell therapy.

In some embodiments of any of the methods disclosed herein, the responder (for example, the complete or partial responder) has one, two, three or more (or all) of the following profile:

- (i) has a greater number of CD27+ immune effector cells compared to a reference value, for example, a non-responder number of CD27+ immune effector cells;
- (ii) has a greater number of CD8+ T cells compared to a reference value, for example, a non-responder number of CD8+ T cells;
- (iii) has a lower number of immune cells expressing one or more checkpoint inhibitors, for example, a checkpoint inhibitor chosen from PD-1, PD-L1, LAG-3, TIM-3, or KLRG-1, or a combination, compared to a

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reference value, for example, a non-responder number of cells expressing one or more checkpoint inhibitors; or

(iv) has a greater number of one, two, three, four or more (all) of resting  $T_{EFF}$  cells, resting  $T_{REG}$  cells, naïve CD4 cells, unstimulated memory cells or early memory T cells, or a combination thereof, compared to a reference value, for example, a non-responder number of resting  $T_{EFF}$  cells, resting  $T_{REG}$  cells, naïve CD4 cells, unstimulated memory cells or early memory T cells.

In embodiments, a subject who is a responder, a non-responder, a relaper or a non-relapser identified by the methods herein can be further evaluated according to clinical criteria. For example, a complete responder has, or is identified as, a subject having a disease, for example, a cancer, who exhibits a complete response, for example, a complete remission, to a treatment. A complete response may be identified, for example, using the NCCN Guidelines®, or the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) 2018 guidelines as disclosed in Hallek M et al., Blood (2018) 131:2745-2760 “iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL,” the entire contents of which are hereby incorporated by reference in its entirety. A partial responder has, or is identified as, a subject having a disease, for example, a cancer, who exhibits a partial response, for example, a partial remission, to a treatment. A partial response may be identified, for example, using the NCCN Guidelines®, or iwCLL 2018 criteria as described herein. A non-responder has, or is identified as, a subject having a disease, for example, a cancer, who does not exhibit a response to a treatment, for example, the patient has stable disease or progressive disease. A non-responder may be identified, for example, using the NCCN Guidelines®, or iwCLL 2018 criteria as described herein.

Alternatively, or in combination with the methods disclosed herein, responsive to said value, performing one, two, three four or more of:

- administering for example, to a responder or a non-relapser, a CAR-expressing cell therapy;
- administered an altered dosing of a CAR-expressing cell therapy;
- altering the schedule or time course of a CAR-expressing cell therapy;
- administering, for example, to a non-responder or a partial responder, an additional agent in combination with a CAR-expressing cell therapy, for example, a checkpoint inhibitor, for example, a checkpoint inhibitor described herein;
- administering to a non-responder or partial responder a therapy that increases the number of younger T cells in the subject prior to treatment with a CAR-expressing cell therapy;
- modifying a manufacturing process of a CAR-expressing cell therapy, for example, enriching for younger T cells prior to introducing a nucleic acid encoding a CAR, or increasing the transduction efficiency, for example, for a subject identified as a non-responder or a partial responder;
- administering an alternative therapy, for example, for a non-responder or partial responder or relapser; or if the subject is, or is identified as, a non-responder or a relapser, decreasing the  $T_{REG}$  cell population and/or  $T_{REG}$  gene signature, for example, by one or more of

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CD25 depletion, administration of cyclophosphamide, anti-GITR antibody, or a combination thereof.

## EXAMPLES

The invention is further described in detail by reference to the following experimental examples. These examples are provided for purposes of illustration only, and are not intended to be limiting unless otherwise specified. Thus, the invention should in no way be construed as being limited to the following examples, but rather, should be construed to encompass any and all variations which become evident as a result of the teaching provided herein.

**Example 1: In Vitro Characterization of Human BCMA CARs**

A set of fully human single chain variable fragments (scFv) was cloned into lentiviral CAR expression vectors with the CD3zeta chain and the 4-1BB stimulatory molecules: R1B6, R1F2, R1G5, PI61, B61-10, B61-02, Hy03, and Hy52. The constructs were initially screened using automated cell reporter assay followed by selection for optimal clones based on expression on primary T cells as well as quantity and quality of effector T cell responses ("BCMA CART" or "BCMA CAR T cells") in response to BCMA expressing ("BCMA+" or "BCMA positive") targets. Effector T cell responses include, but are not limited to, cellular expansion, proliferation, doubling, cytokine production and target cell killing or cytolytic activity (degranulation).

**Generation of BCMA CAR Lentivirus**

All the above-mentioned scFv encoding lentiviral transfer vectors were used to produce the genomic material packaged into the VSVg pseudotyped lentiviral particles. Lentiviral transfer vector DNA encoding the CAR was mixed with the three packaging components VSVg, gag/pol and rev in combination with lipofectamine reagent to transfect Lenti-X 293T cells (Clontech), followed by medium replacement 12-18 h later. 30 hours after medium change, the media was collected, filtered and stored at -80° C.

**BCMA CAR JNL and JNL Screening Reporter Assay Using Automated System**

For the reporter assay, lentivirus encoding for BCMA CARs was generated in HEK293 cells at two different cell densities (40,000 cells (1×H293) or 80,000 cells (2×H293)) in an automated, small scale fashion in 96-well plates, where virus-containing supernatant was harvested 48 h after transfection and used fresh, without freezing, for the transduction of a Jurkat T cell reporter cell line. The Jurkat NFAT Luciferase (JNL) reporter cell line is based on the acute T cell leukemia line Jurkat. The line was modified to express luciferase under control of the Nuclear Factor of Activated T cells (NFAT) response element. For the transduction with BCMA CARs, 10,000 JNL cells/well of a 96-well plate were transduced with 50 µl of fresh, 45 pm-filtered virus-containing supernatant. The plates were cultured for 5 days before co-culturing with target cells.

To evaluate the functional ability of BCMA CARs to activate JNL cells, they were co-cultured with target cancer cells at different effector to target cell ratios (E:T ratio) to read out their activation by quantifying luciferase expression. The scFv-based CARs R1B6, R1F2, R1G5, PI61, B61-10, B61-02, Hy03, and Hy52 were assessed. The CD19 JNL CAR cells were used as a target specific control, and media alone without target cells served as a negative control.

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The above mentioned five-day transduced JNL CAR cells were co-cultured with the BCMA-positive multiple myeloma (MM) cell line KMS11, or NALM6, an acute lymphocytic leukemia cell line, served as a BCMA-negative control. Remaining JNL CAR T cells were evaluated for BCMA CAR expression by flow cytometry. Co-cultures were set up in 384-well plates at effector-to-target (E:T) ratios of 4:1, 2:1, 1:1 and 0.5:1 and incubated for 24h, after which the expression of luciferase by the activated JNL CAR T cells was quantified by Bright-Glo™ Luciferase Assay System (Promega, Madison, WI). The amount of light emitted from each well (luminescence) was a direct read-out of JNL activation by the respective CAR. JNL cells were considered to be activated when the level of luminescence was equal or more than twofold of UTD cells. The BCMA+ KMS11 cell line led to activation of the JNL cells expressing R1B6, R1F2, R1G5, PI61, B61-10, B61-02, Hy03, and Hy52 (FIGS. 1A and 1C). None of the BCMA CARs showed activation by the BCMA-negative line NALM6 (FIGS. 1E and 1F). Media alone, without target cells, did not activate any of the CAR transduced JNLs tested (FIGS. 1G and 1H). FACS analyses demonstrated that BCMA-CAR expression in transduced JNLs was detected to different degrees; CAR % is generally positively correlated with JNL activation by KMS11 cells in the most active JNL CARTs (FIGS. 1B and 1D).

**Generation of BCMA CAR T Cells**

The following 8 CARs were chosen for analysis of CAR expression, stability and efficacy in primary T cells: R1B6, R1F2, R1G5, PI61, B61-10, B61-02, Hy03, and Hy52. BCMA CAR T cells were generated by starting with blood from healthy apheresed donors whose T cells (CD4+ and CD8+ lymphocytes) were obtained by negative selection for CD3+ T cells. These cells were activated by the addition of CD3/CD28 beads (Dynabeads® Human T-Expander CD3/CD28, Thermo Fisher Scientific) at a ratio of 1:3 (T cell to bead) in T cell medium (RPMI1640, 10% heat-inactivated fetal calf serum (FCS), 2 mM L-glutamine, 1x Penicillin/Streptomycin, 100 µM non-essential amino acids, 1 mM Sodium Pyruvate, 10 mM Hepes, and 55 µM 2-mercaptoethanol). T cells were cultured at  $0.5 \times 10^6$  T cells in 1 mL medium per well of a 24-well plate at 37° C., 5% CO<sub>2</sub>. After 24 hours, when T cells were blasting, T cells were transduced with BCMA CAR virus at a multiplicity of infection (MOI) of 5. T cells began to divide in a logarithmic growth pattern, which was monitored by measuring the cell counts per mL, and T cells were diluted in fresh medium every two days and de-beaded and harvested for further analyses at day 9. Aliquots of T cells were stained to measure CAR expression by flow cytometry at day 5 and 9 on a FACS Fortessa (BD). All BCMA CAR T cells were produced under research grade (i.e., not clinical grade) manufacturing conditions.

The BCMA-CAR surface expression and its stability was assessed by measuring CAR % and MFI (mean fluorescence intensity) at day 5 and day 9 using flow cytometry analyses of rBCMA\_Fc-AF647 stained cells (FIG. 2 and Table 27). BCMA CAR expression in the final product at day 9 differs from construct to construct, ranging from 18% to 42.4%, and MFI from 672 to 5238. Constructs from PALLAS-derived clones R1F2, R1B6, and R1G5, and the hybridoma clone, Hy03 showed ~30% to 50% CAR loss from day 5 to day 9, while PI61, B61-10 and -02, as well as Hy52 are relatively stable in terms of the percentage of CAR expression, though all the CAR constructs showed a decrease in MFI from day 5 to day 9, which was probably due to the smaller size of T cells at their resting stage on day 9. The cell counts of the CAR T cell cultures indicated that there is no detectable

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negative effect of the human scFv bearing BCMA CAR on the ability of the cells to expand normally when compared to the untransduced T cells (“UTD”).

TABLE 27

Analysis of CAR expression					
CAR		CAR % on T cells	CAR MFI on T cells		
Construct	Titer	Day 5	Day 9	Day 5	Day 9
R1B6	2.68E+08	40.0	27.4	24,420	2,367
R1F2	3.60E+08	48.8	22.7	4,716	672
R1G5	2.27E+08	52.0	30.7	29,113	5,238
PI61	1.71E+08	47.4	42.3	24,360	2,099
B61-10	7.06E+07	41.1	30.3	27,298	3,288
B61-02	8.16E+07	33.5	23.6	29,113	3,471
Hy03	4.96E+07	33.7	18.1	9,463	929
Hy52	7.03E+07	35.1	36.1	33,694	2,859

#### Evaluating Functionality of BCMA CAR-Redirected T Cells

To evaluate the functional abilities of BCMA CAR-T cells, co-cultures were set up with BCMA-positive and -negative cancer lines. CAR-T cells were thawed, counted and co-cultured with target cells to read out their killing capabilities and secretion of cytokines. BCMA CAR-clones R1B6, R1F2, R1G5, B61-02, B61-10, PI61, Hy03, and Hy52 were tested. Non-transduced T cells (UTD) were used as non-targeting T cell controls.

CART cell killing was performed by co-culturing CART cells with KMS11-Luc and NALM6-Luc target cells at different E:T ratios for 20 hours. CAR T cell populations were normalized to equivalent percentages of CAR-positive cells before plating. The cytokine IFN $\gamma$  was measured in supernatants from 20 hour co-cultures of CAR-T cells with target cells at effector to target ratio of 2.5:1 using the Meso Scale Discovery (MSD; Gaithersburg, MD) and the results for each cytokine were calculated in pg/ml using known standards. All assays were performed in duplicate from a single source of donor cells. Killing data shows that all the BCMA CAR clones kill KMS11 cancer cells effectively (FIG. 3A). The control target cell NALM6 was not killed by any of these BCMA-specific CARs (FIG. 3B). The ability of these CARs to produce IFN- $\gamma$  when cultured with KMS11 was also tested (FIG. 3C). BCMA CAR R1F2, R1G5 and PI61 led to the highest amounts of IFN- $\gamma$  being produced. Levels of cytokine produced by BCMA CARTs after exposure to the control NALM6 cells were low (FIG. 3C), indicating no unspecific activation by BCMA CARs.

#### Conclusions

New BCMA-binding scFvs were tested in the context of CAR T cells. Eight CARs were assayed in a JNL reporter assay as well as in primary T cells: R1B6, R1F2, R1G5, B61-02, B61-10, PI61, Hy03, and Hy52. All eight CAR-T cells showed target-specific killing. T cells expressing R1F2, R1G5, or PI61 produced the highest amounts of IFN- $\gamma$  in the presence of target cells. Overall, the transfer of BCMA CARs to primary T cells induced anti-BCMA CAR reactivity but no off-target function.

#### Example 2: Dual CAR Expression and In Vitro Activity of Anti-BCMA and Anti-CD19 Dual CARTs

A set of bicistronic constructs comprising two full CAR (chimeric antigen receptor) chains, one directed to BCMA and the other to CD19, was engineered in a lentiviral vector (Table 28). CAR expression is driven by the EF1alpha

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promoter. Such CARs comprise a set of human single chain variable fragments (scFv) targeting BCMA (duBCMA.4, PI61, R1G5, and R1B6). The same humanized scFv targeting CD19 was engineered in all the constructs. At the N-terminus of each scFv, a signal peptide derived from CD8 alpha targets the CAR to the secretory pathway. Such a signal peptide is expected to be cleaved co-translationally and therefore be absent in the mature form of the CAR displayed at the cell surface. At the C-terminus of each scFv 10 is the hinge and transmembrane domain of CD8 alpha, fused to the intracellular domain of 4-1BB, followed by the intracellular domain of CD3zeta. Between the two CARs, more precisely between the last amino acid of the first CD3zeta domain and the signal peptide of the subsequent 15 CAR, is engineered a linker (GSG (SEQ ID NO: 206)) followed by 2A self-cleaving peptide from porcine teschovirus-1 2A (i.e., P2A sequence). Other linkers and/or self-cleaving peptides could be used as well. This design affords expression of two independent CARs, from a single mRNA 20 transcript. The DNA sequences encoding the overlapping regions between the two CARs (signal peptide, hinge, transmembrane domain, 4-1BB, and CD3zeta) are distinct from one another in order to minimize potential recombination.

TABLE 28

Summary of constructs.	
Construct NO.	Description
234	duCD19.1-duBCMA.4
235	duBCMA.4-duCD19.1
236	R1G5-duCD19.1
237	R1B6-duCD19.1
238	PI61-duCD19.1
244	Mono-duCD19.1
245	Mono-duBCMA.4

The constructs were used to make vector material, which was used to infect human primary T cells. CAR expression 40 was assessed by flow cytometry. The quantity and quality of effector T cell responses (“BCMA-CD19 dual CART” or “T cells”) in response to BCMA expressing (“BCMA+” or “BCMA positive”) and CD19+ tumor targets were also measured. Effector T cell responses include, but are not limited to, cellular expansion, proliferation, doubling, cytokine production and target cell killing or cytolytic activity (degranulation).

#### Lentivirus Production and Titer Determination

The five constructs, encoding the dual BCMA/CD19 50 CARs, described above were used to produce genomic material packaged into VSVg pseudotyped lentiviral particles. Two constructs were used as controls: one encoding a mono CAR directed against BCMA (duBCMA.4) and another encoding a mono CAR directed against CD19. All 55 seven constructs were engineered in the same plasmid backbone. Each of these DNAs was mixed with the three packaging components VSVg, gag/pol and rev in combination with lipofectamine reagent to transfect Lenti-X 293T cells (Clontech), followed by medium replacement 12-18 h later. 30 hours after medium change, the media was collected, filtered and stored at -80° C.

Lentiviral titer was determined by evaluating the surface 60 expression of BCMA-CD19 dual CARs on transduced Sup-T1 cells using recombinant human Alexa-647-Fc-tagged BCMA protein (BCMA-Fc) and antiID-ducCD19.1 antibody (PE). Sup-T1 cells were transduced with a 3-fold serial dilution of viral supernatants with a starting dilution of 1:3.

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The percentage of cells expressing the CAR (CAR+ cells) was assessed four days later. Viral titer was calculated either using the upstream CAR positivity or dual positive CAR population according to the following formula:

$$\frac{(\% \text{ CAR+}) \times (\# \text{Sup-T1 cells seeded}) \times (\text{Dilution})}{(\text{Amount of Virus (mL)})}$$

Viral titer was calculated from the central most dilution point in the linear range giving between 5 and 25% CAR+ cells (Table 29).

TABLE 29

Construct NO.	supT1 titers.	
	Based on CAR+ of the upstream CAR (a)	Based on the double+ CAR (b)
234	5.39E+07	1.91E+07
235	4.41E+08	1.15E+08
236	2.14E+08	1.17E+08
237	1.97E+08	8.51E+07
238	1.85E+08	5.66E+07

#### Generation of BCMA-CD19 CAR T Cells Using Conventional 10-Day Production Process

BCMA-CD19 dual or monoBCMA or monoCD19 CART cells were generated using human primary T cells (CD4+ and CD8+ lymphocytes) obtained by negative selection or positive selection via Prodigy upon processing blood from healthy apheresed donors. Before transduction, the T cells were activated using CD3/CD28 beads (Dynabeads® Human T-Expander CD3/CD28, Thermo Fisher Scientific) at a ratio of 1:3 (T cell to bead) in T cell medium (RPMI1640, 10% heat-inactivated fetal calf serum (FCS), 2 mM L-glutamine, 1× Penicillin/Streptomycin, 100 µM non-essential amino acids, 1 mM Sodium Pyruvate, 10 mM Hepes, and 55 µM 2-mercaptoethanol). The cells were cultured at a density of  $0.5 \times 10^6$ /mL medium per well in a 24-well plate at 37° C., 5% CO<sub>2</sub>. After 24 hours, when T cells were blasting, they were transduced with viruses at a multiplicity of infection (MOI) of 5 based on the upstream CAR titer. T cells began to divide in a logarithmic growth pattern, which was monitored by measuring the cell counts per mL, and T cells were diluted in fresh medium every two days and de-beaded and harvested for further analyses on day 8 or beyond depending on the size of the cells. Aliquots of T cells were stained to measure CAR expression by flow cytometry on day 7 or 8 on a FACS Fortessa (BD).

The BCMA-CAR and CD19-CAR surface expression was assessed by measuring CAR % and MFI (mean fluorescence intensity) at day 8 using flow cytometry analyses of rBCMA\_Fc-AF647 and antiID-duCD19.1 (PE) stained cells (FIGS. 4A-4C). The three dual CAR vectors comprising R1G5, R1B6, or PI61 led to a similar percentage of double positive CARs (~10%), with construct 236 (R1G5/duCD19.1) displaying the highest MFI levels for BCMA and CD19 CARs (FIG. 4A). The mono duCD19.1 (construct 244) displays the highest MFI for CAR19 across the different constructs (FIG. 4B).

#### Evaluating Functionality of Dual BCMA-CD19 CAR-Directed D8 T Cell Product In Vitro and In Vivo

To evaluate the anti-tumor efficacy of each of the CARs within the dual BCMA-CD19 CART cells, co-cultures were set up with BCMA positive (KMS11), CD19 positive (NALM6) and BCMA/CD19 negative cancer lines (CD19KO; NALM6-derived). CART cells were thawed, counted and co-cultured with target cells to read out their

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killing capabilities and secretion of cytokine. Non-transduced T cells (UTD) were used as non-targeting T cell controls.

The in vitro cytotoxic assay was performed by co-culturing CART cells with target cells expressing luciferase at different E:T ratios for 20 hours. CART cell populations were normalized to equivalent percentages of CAR-positive cells before plating, according to the CAR directed to the respective tumor (i.e., normalization based on BCMA CAR when CARTs were co-cultured with KMS11 cells; and normalization based on CAR19 when CARTs were co-cultured with NALM6). The cytokine IFNγ was measured in the supernatants of the 20-hour co-cultures, corresponding to a target ratio of 1.25:1 or 2.5:1 (CAR-T cells: target cells), using the Meso Scale Discovery (MSD; Gaithersburg, MD). The results were calculated in pg/mL using known standards. All assays were performed in duplicate from a single source of donor cells. Killing data show that all dual CAR clones were effective against BCMA-positive KMS11 cells and CD19-positive Nalm6 cells (FIGS. 5A and 5B, respectively). Only background killing was observed against the BCMA/CD19 negative tumor cells (FIG. 5C). The ability of these dual CARs to produce IFN-γ when co-cultured with KMS11 or Nalm6 was similar as assessed using two different E:T ratios (FIGS. 6A-6D).

The in vivo anti-tumor activity of these D8 CARTs is analyzed using mixed xenograft tumor model (5% Nalm6 and 95% KMS11) in NSG mice. 30 Production and Measurement of Day 1 Anti BCMA-CD19 Dual CARTs with Activated Rapid Manufacturing (ARM) Process In some embodiments, this ARM process starts with a frozen or fresh leukapheresis product.

After a sample for counting and QC is obtained, the product is attached to a cell sorting machine (e.g., an installed CliniMACS Prodigy device kit) and the program begins. The cells are washed and incubated with microbeads that bind to desired surface markers, such as CD4 and CD8. The bead-labeled cells are selected by passing the cells through a magnetic column. Isolated cells are washed again and the separation buffer is exchanged for cell media. Purified T cells then either proceed to culture or are cryopreserved for later use. Purity of the isolated T cells will pass a QC step by flow cytometry assessment. Cryopreserved cells are thawed, washed in pre-warmed cell media, and resuspended in cell media. Fresh cells are added to culture directly. The cells are seeded into membrane bioreactors at 0.4-1.2e6 cells/cm<sup>2</sup> of membrane, an activating reagent such as anti-CD3/anti-CD28 beads/polymers, nanoparticles, or nanocolloids is added, and cell media is added to a final volume of 0.25-2 ml/cm<sup>2</sup> of membrane. For in vitro CAR expression kinetics study, a 24 well Grex is used. A Grex100, flask, or centricult is used to test whether this manufacturing process is scalable and to test in vivo anti-tumor efficacy. At the time of plating, the cells are transduced with a lentiviral vector encoding BCMA-CD19 dual CAR at a multiplicity of infection (MOI) of 1 or 2. MOI is determined based on the viral titer obtained in SupT1 cells, basing on the titer of the CAR that is engineered upstream of the 2A sequence. At 24 hours, the cells are washed to remove unnecessary reagents before staining to measure the CAR expression by flow cytometry and reformulated in cryopreservation media as “day 1 CART product” for in vivo study. In all cases, an aliquot of cells is harvested at 72 h post transduction for measuring CAR expression kinetics in vitro. The day 1 CART responses include, but are not limited to, in vivo cytolytic activity and expansion.

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FIGS. 7A-7B show the expression pattern of both anti-BCMA and anti-CD19 CARs, at 24 h and 72 h post-transduction of human primary T cells manufactured using the ARM process, using a MOI of 1 based on the SupT1 titer determined by expression of the upstream CAR only. Twenty-four hours post-transduction, it was observed in a flow cytometry analysis that the whole population of live CD3+ T cells shifted to the right at different degrees (FIG. 7A). This expression pattern was different from a typical flow cytometry histogram of cells transduced to express a CAR, where a CAR positive population is clearly separated from a negative population. These data suggest “pseudotransduction or transient expression” may be detected by the rBCMA\_Fc flow cytometry staining reagent. It has been previously reported that lentiviral pseudotransduction was observed from the time of vector addition to 24 hours in CD34+ cells and up to 72 hours in 293 cells (Haas D L, et al. Mol Ther. 2000; 291: 71-80). Integrase-defective lentiviral vector caused transient eGFP expression for up to 10 days in CD34+ cells and for up to 14 days in 293 cells. Although the observed CAR expression on day 1 post T cell transduction may be potentially attributed to pseudotransduction, on day 3, however, two clear populations emerged, one that was rBCMA\_Fc positive and the other anti-ID duCD19.1 positive (FIG. 7B and FIG. 7C). Furthermore, 20 to 30% of cells were monoBCMACAR positive (CD19CAR negative) in cells engineered using the dual constructs c235, c236, c237, and c238 (FIG. 7C). Altogether, these results demonstrate that both CARs were well expressed in the dual CART system when R1G5, R1B6, and PI61 were used in combination with duCD19.1. 72 h post viral transduction could serve as a surrogate time point for measuring CAR expression for *in vivo* dosing strategy.

#### Evaluating Functionality of the Day 1 ARM Processed BCMA CART In Vivo

The day 1 CARTs generated using the centrifuge or flask system were examined for their anti-tumor activity *in vivo* using three mouse models: a disseminated KMS-11-luc (BCMA+CD19-) multiple myeloma model, a Nalm6-Luc (CD19+BCMA-) xenograft mouse model, and a mixed model of 95% KMS-luc with 5% NALM6-Luc cells. The aims of this *in vivo* study was threefold: (1) demonstrating efficacy of both the BCMA and CD19 arms of the dual CARTs; (2) comparing the mixed model (comprising BCMA+ tumor cells and CD19+ tumor cells) to the KMS-11-luc multiple myeloma model (BCMA+CD19-) to understand potential activation of the dual CARTs through the CD19 target; and (3) testing the dual CARTs in the Nalm6 alone model (CD19+BCMA-) to examine the activity of the CD19 arm. BLI measurements were taken twice weekly. Peripheral blood was taken at days 6, 13, 20 and 27 for flow cytometry analysis. Plasma was collected on previously mentioned days along with day 2 for cytokine analysis. The study design and dose information are summarized in Table 30.

TABLE 30

In vivo study design and dose regime			
	KMS11 (BCMA)	Nalm6 (CD19)	Both Luc tagged KMS11 (BCMA) and Nalm6 (CD19) mix
c236	1e4, 5e4	1.5e5	1e4, 5e4
c238	1e4, 5e4	1.5e5	1e4, 5e4
Mono PI61	1e4, 5e4	1e4, 5e4	1e4, 5e4
Mono CTL119		1.5e5	1e4, 5e4

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The dual CARTs cleared mixed tumors (BCMA+CD19+) at the dose of 5e4, and inhibited but not fully eliminated tumors at the dose of 1e4 over the course of the study (FIG. 8C). Neither PI61 nor CTL119 could control the mixed tumor (FIG. 8C). Both duals c236 and c238 exhibited similar or superior efficacy compared to the mono counterparts in the KMS11 and Nalm6 models (FIGS. 8A and 8B). Body weights increased during the study in all three models (FIGS. 9A-9C). There was a slight drop at the end of the KMS11 and NALM6 study possibly due to GVHD.

T cell expansion occurred from Day 6 to Day 20, and then evened out from Day 20 to Day 27 (FIGS. 10A-10C). Expansion was dose related across all three models (FIGS. 11A-11C). The KMS11 model showed 3-4 folds higher expansion compared to the mixed model in the higher doses (FIGS. 10A and 10C). Duals c236 and c238 showed higher expansion than mono CARTs (FIGS. 10A-10C).

Total BCMA CAR+ percentage peaked at Day 13 and then began to decrease through Day 27 (FIGS. 11A-11C). In the mixed model, the 5e4 groups showed lower BCMA CAR+ percentages compared to the 1e4 groups after Day 13 (FIG. 11C). The double CAR+ percentage was related to an influx of total CD3+ cells, which could be a possible sign of GVHD. Double anti-BCMA and CD19 CAR+ T cell expansion was observed in c236 and c238 CART Rx groups in all three models (FIGS. 12A-12C).

Induction of IFN $\gamma$  was dose responsive across all the models (FIGS. 13A-13C). Duals at both doses produced ~3 to 4 folds more IFN $\gamma$  at peak in the mixed model than that in the KMS11 alone model (FIGS. 13A and 13C). Peak induction was observed within 13 days in most of the groups in all the models (day 20 and day 27 peaks were most likely due to GVHD) (FIGS. 13A-13C).

In a separate study, the day 1 CARTs generated using Grex100 and 6-well Grex system were examined for their anti-tumor activity *in vivo* using a disseminated KMS-11-luc multiple myeloma model. The luciferase reporter allows for monitoring of disease burden by quantitative bioluminescence imaging (BLI). Briefly, day 1 CARTs manufactured as described above were administered in tumor-bearing mice. Blood samples were taken weekly to measure peripheral blood CART expansion and analyzed by flow cytometry. T cells engineered with construct #236 and construct #238 displayed potent anti-tumor activity (FIG. 14A) and good CART expansion (FIG. 14B) *in vivo* towards a KMS11 (BCMA+CD19-) model.

#### Example 3: Characterization of Diabody CARTs

This example describes characterization of diabody CARs JL1 to JL10. JL1 to JL8 are PI61/CTL119 diabody constructs and JL9 to JL10 are R1G5/CTL119 diabody constructs. The sequence information of JL1 to JL10 is disclosed in Table 31.

#### 55 Production and Measurement of Day 1 Anti BCMA-CD19 Diabody CARTs with Activated Rapid Manufacturing (ARM) Process

In some embodiments, this ARM process starts with a frozen or fresh leukapheresis product. After a sample for counting and QC is obtained, the product is attached to a cell sorting machine (e.g., an installed CliniMACS Prodigy device kit) and the program begins. The cells are washed and incubated with microbeads that bind to desired surface markers, such as CD4 and CD8. The bead-labeled cells are selected by passing the cells through a magnetic column. Isolated cells are washed again and the separation buffer is exchanged for cell media. Purified T cells then either pro-

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ceed to culture or are cryopreserved for later use. Purity of the isolated T cells will pass a QC step by flow cytometry assessment. Cryopreserved cells are thawed, washed in pre-warmed cell media, and resuspended in cell media. Fresh cells are added to culture directly. Aliquots of frozen Pan T isolated cells are thawed in a 37° C. water bath, put into Optimizer CM (Gibco Optimizer Media with Supplement+100U/mL human IL2) and spun for 5 minutes at 1500 rpm. Cells are counted and plated into a 24-well plate at 3e6/mL, 1 mL/well. TransAct is added to each well at 1/100 (10 µL/well).

For in vitro CAR expression kinetics study with the ARM process, a 24-well plate was used. At the time of plating, the cells were transduced with a lentiviral vector encoding BCMA-CD19 diabody CAR at a multiplicity of infection (MOI) of 2. MOI was determined based on the viral titer obtained in SupT1 cells based on the double positive CAR expression. After 24 hours in culture, cells were harvested and washed three times in PBS+1% HSA. Cells were then counted and re-plated at 1e6/mL final in a 24-well plate. 72 hours after re-plating, cells were harvested, counted and an aliquot of 5e5 cells from each sample was taken for flow cytometry analysis. This procedure was repeated 72 hours later for a day seven time point.

FIGS. 15A and 15B show the expression pattern of both anti-BCMA and anti-CD19 CARs, at 96 h (FIG. 15A) or 7 days (FIG. 15B) post-diabody viral addition to human primary T cells manufactured using the ARM process, using a MOI of 2. Altogether, these results demonstrate that both CARs were well expressed in the diabody CART system when R1G5 or PI61 was used in combination with duCD19.1 on day 4 (FIG. 15A) or day 7 (FIG. 15B) post viral addition. JL1-JL4, JL9, and JL10 showed linear expression of the double positive CAR, while JL5-JL8 showed a slight shift towards CD19+ population, which could be due to CAR binding differences to its respective detecting reagents. Data from one of two donors are shown here.

CAR-T cells production using Traditional manufacturing process Traditional manufacturing (TM) process is a process where T cells are expanded ex vivo for 8 to 9 days after activation and transduction prior to harvest. Prodigy processed T cells were resuspended in warm RPMI complete T cell medium (RPMI, 10% heat-inactivated FBS, 2 mM L-Glutamine, 100 U/mL Pen/Strep, 1×NEAA, 1 mM Sodium Pyruvate, 10 mM HEPES, and 55 µM P-Mercaptoethanol), and plated in 24-well plates at 0.5e6 cells/mL per well. T cells were incubated overnight at 37° C. with Human T-Expander CD3/CD28 beads at a 3:1 ratio of beads-to-

cells.

On Day 1, lentiviruses were added at a MOI of 5, based on the SUP-T1 titer. No virus was added to the untransduced control (UTD). The T cells were incubated overnight at 37° C. followed by the addition of 1 mL complete T cell medium per well, after which they were incubated overnight at 37° C. For the remaining six days of culture expansion, the T cells were transferred into tissue culture flasks and diluted with complete T cell medium every two days, targeting a concentration of 0.5e6 cells/mL. Typical split ratios ranged from 1:2 to 1:4 during the expansion phase.

On Day 7, the T cells were de-beaded, harvested and cryopreserved in CryoStor CS10 freezing medium, frozen at -80° C. in CoolCell Cell Freezing Containers (Biocision), and transferred to LN<sub>2</sub> the following day. Small aliquots of T cells were stained for CAR expression. Single color controls were included for compensation. Samples were

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measured on a flow cytometer (BD LSRII Fortessa), and data were analyzed with FlowJo software.

FIG. 16 demonstrates CAR Expression at day 7 with TM process using MOI of 5. The TM products showed a similar expression pattern as the ARM products (FIGS. 15A, 15B, and 16).

## In Vitro Killing Assay

The killing potential of T cells engineered with various diabody constructs in response to BCMA or CD19 expressing target cells was evaluated by incubating CART cells with target cells at 2-fold E:T ratio dilutions starting at 20:1. The number of target cells were fixed at 2.5×10<sup>5</sup> cells/well and cells were cultured in 96-well flat-bottom plates. Effector cells were CART cells generated using traditional manufacturing by transducing T cells with diabodies. Target cells include BCMA positive KMS11-luc cells or BCMA negative NALM6-luc cells. For this assay, the % transduction of CAR-T cells was normalized by addition of UTD to the BCMA CARTs. This allowed for the comparison of the same number of CARTs and same total T cell number in each sample.

Loss of luciferase signal resulting from cell killing was measured using Bright-Glo substrate 16h after cell seeding and specific lysis was calculated according to the following formula:

$$\text{Specific lysis (\%)} = 100 - (\text{sample luminescence} / \text{average maximal luminescence}) * 100$$

FIGS. 17A and 17B demonstrate the ability of different diabodies of PI61/CTL119 to effectively kill specific target cell lines NALM-6 (CD19+, BCMA-) (FIG. 17A) or KMS-11 (CD19-, BCMA+) (FIG. 17B). The data suggest that clones JL6, JL5, JL3, and JL8 equally killed both target cells.

## Cytokine Secretion Assay

Supernatants were collected from the co-cultures (a ratio of 1.25:1) used in the killing assay above after 20 h incubation to be used in the MSD V-PLEX Human IFN-□□ and IL-2 analysis. Different magnitude of target-specific induction of IFN-□ or IL-2 by diabody transduced cells was observed in response to stimulation with KMS11 or NALM6 cells (FIGS. 18A and 18B). UTD cells did not show any unspecific IFN-□□ secretion in response to either target cells (FIG. 18A). In line with the results from the killing assay, clones JL6, JL5, JL3, and JL8 produced more cytokines in response to the target cells (FIGS. 18A and 18B).

## Example 4: Co-Transduction of BCMA CAR and CD19 CAR

Aliquots of frozen Pan T isolated cells were thawed in a 37° C. water bath, put into Optimizer CM (Gibco Optimizer Media with Supplement+100U/mL human IL2) and spun for 5 minutes at 1500 rpm. Cells were counted and plated into a 24-well plate at 3e6/mL, 1 mL/well. TransAct was added to each well at 1/100 (10 µL/well). Virus was added at differing multiplicity of infections (MOIs) based on either the SupT1 titer for PI61 or the qPCR titer for CTL119. PI61 was used at a MOI of 2 or 1 and paired with three different CTL119 MOIs: 1, 0.5, and 0.25. Mono CARs were added at a MOI of 1 or 2 for PI61 and 1 for CTL119, and a UTD control was plated as well. After 24 hours in culture, cells were harvested and washed three times in PBS+1% HSA. Cells were then counted and re-plated at 1e6/mL final in a 24-well plate.

72 hours after re-plating, cells were harvested, counted and an aliquot of 5e5 cells from each sample was taken for

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flow cytometry analysis. Cells were stained with Live/Dead Aqua (BV510) for 15 minutes in 100 µl/well and were then washed twice. The antibody MM (Table 32) was then added at 50 µl/well for 25 minutes at 4°C. Cells were washed twice again and then fixed for 15 minutes in 1.6% PFA in PBS, 100 µl/well. After fixing, cells were washed as previously described and resuspended in a final volume of 150 µl/sample in flow cytometry buffer. 5e4 cells were acquired on the Live CD3 positive gate of each sample on a BD LSRFortessa (BD Biosciences, San Jose CA) and data was analyzed using FlowJo v.10 software (Ashland, OR). This procedure was repeated 72 hrs later for a day seven time point.

TABLE 32

Antibody and other reagents.					
Marker	Clone	Fluorochrome	Vendor	Catalogue No.	Dilution
Live/Dead		BV510	Biolegend	423102	1/500
CD3	SK7	BUV395	BD	564001	1/200
CAR19	Anti-ID	PE	In House Reagent		1/160
CD4	SK3	PerCP 5.5	Biolegend	344608	1/100
CAR	rBCMA FC	AF 647	In House Reagent		1/380 (3 ug/ml)
CD8	SK1	APC H7	BD	560179	1/200
	FACS Buffer		Miltenyi Biotec	130-091-222	
	BSA Stock Solution		Miltenyi Biotec	130-091-376	
	Phosphate Buffer Saline (PBS)		Gibco	14190-144	
	Para formaldehyde (PFA)		Polysciences Inc.	18814-10	

At Day four after viral addition, flow cytometry analysis showed significantly higher percentages of mono BCMA CAR+ population over the CAR19 positive population and the double CAR positive population in the BCMA CAR MOI 2 conditions (FIGS. 19 and 20). This was consistent across both donors. When PI61 was added at a MOI of 1, good titration of all the populations was observed (FIGS. 19 and 20). CAR19+ population as well as the double CAR+ population decreased as the CD19 CAR MOI decreased from 1 to 0.25 (FIG. 19). The BCMA CAR+ population increased when the CTL119-encoding virus was added at a lower amount (FIG. 19). Total CAR+ populations correlated in percentages with the total MOI added to each well (FIG. 21). Total BCMA CAR and CAR19 percentages correlated

30 day of production (Day 0) by means of anti-CD4/anti-CD8 immunomagnetic system. Positive fraction is then seeded in G-rex culture vessel, activated with an anti-CD3/CD28 system (TransACT) and on the same day transduced with a lentiviral vector (LV) encoding a CAR. On the following day, after 20-28 hours of transduction, the T cells are harvested, washed four times, formulated in freezing medium and then frozen by a Controlled Rate Freezer (CRF). From the start of the process on Day 0 to the 35 initiation of harvest on the following day, cells are cultured for 20-28 hours with a target of 24 hours after Day 0 seeding.

40 Media for Day 0 were prepared according to Table 21.

TABLE 21

Media type and point of use during CART manufacturing		
Media/Buffer Type	Composition	Point of Use
Rapid Buffer (RB)	CliniMACS® Buffer (+0.5% human serum albumin (HSA))	Day 0 Processing on Cell Wash/Separator
Rapid Media (RM)	OpTmizer™ Media, CTS™, IL-2, Glutamax and ICSCR	Day 0 for Processing on Cell Wash/Separator and Cell Seeding
Harvest Buffer (HB) (also called Harvest Buffer Solution)	PBS no EDTA and 2% HSA	Harvest Wash Buffer (Day 1)
Cryomedia	Cryostor10 (CS10)	Harvest Formulation

as well. All trends were stable from day four to day seven (FIG. 21). Viability and expansion rates were independent of the total MOI added (FIG. 22). Data from one of the four 60 donors are shown here.

**Example 5: Description of the Activated Rapid Manufacturing (ARM) Process**

In some embodiments, CART cells are manufactured using a continuous Activated Rapid Manufacturing (ARM)

The cryopreserved leukapheresis material is thawed. The thawed cells are diluted with the Rapid Buffer (Table 21) and washed on the CliniMACS® Prodigy® device. The T cells are selected by CliniMACS® CD4 and CD8 microbeads. Once the program is finished for T cell selection (approximately 3 h 40 min to 4 h 40 min), the reapplication bag containing the cells suspended in Rapid Media (Table 21) 65 are transferred in a transfer pack. A sample is taken for viability and cell count. The cell count and viability data

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from the positive fraction bag is used to determine the cell concentration when seeding the culture vessel for activation and vector transduction.

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ucts to obtain T cell percentage target for the apheresis. The results for the T cell percentage determine how many bags are thawed on Day 0 of the ARM process.

TABLE 25

Media and Buffer type and point of use during CART manufacturing		
Media Type	Source	Point of Use
CliniMACS® Buffer/human serum albumin (HSA) (0.5% in working concentration)	Prepared by operator on day 0	Day 0 Processing on Cell Wash/Separator
Rapid Media	Prepared by operator on day 0	Day 0 for Cell Seeding
PBS/HSA (1% or 2% in working concentration)	Prepared by operator on day 0	Harvest and culture Wash Media (Day 1)
Cryostor10 (CS10)	Commercially available	Harvest Formulation

Following positive selection of T cells via the Clinimacs® microbeads (CD4 and CD8), the cells are seeded in the culture vessel, G-Rex. Once the cells are seeded, the activation reagent (TransACT) is then added to the culture vessel. The cells are then transduced with a lentiviral vector encoding a CAR at a target MOI of 1.0 (0.8-1.2). Following the vector addition, the culture vessel is transported to an incubator where it is incubated for a target of 24 hours (operating range 20-28 hours) at a nominal temperature of 37° C. (operating range 36-38° C.) with nominal 5% CO<sub>2</sub> (operating range 4.5-5.5%). Following the incubation, the cells are washed with Harvest Wash Solution (Table 21) four times to remove any non-integrated vector and residual viral particles, as well as any other process related impurities. Then, the cells are eluted and a sample for cell count and viability is taken for testing and the results are used to determine the volume required to re-suspend the cells for final formulation with CryoStor® CS10. The cells are then centrifuged to remove the Harvest Wash Solution and proceed with cryopreservation.

In some embodiments, the CAR expressed in CART cells binds to CD19. In some embodiments, IL-2 used in the Rapid Media (RM) (Table 21) can be replaced with IL-15, heIL-15 (IL-15/sIL-15Ra), IL-6, or IL-6/sIL-6Ra.

In some embodiments, the CAR expressed in CART cells binds to BCMA. In some embodiments, IL-2 used in the Rapid Media (RM) (Table 21) can be replaced with IL-15, heIL-15 (IL-15/sIL-15Ra), IL-6, or IL-6/sIL-6Ra.

In some embodiments, the CART cells express dual CARs disclosed herein, e.g., anti-BCMA/anti-CD19 dual CARs disclosed herein. In some embodiments, the CART cells express a diabody CAR disclosed herein, e.g., an anti-BCMA/anti-CD19 diabody CAR disclosed herein. In some embodiments, the CART cells are engineered to express an anti-BCMA CAR and an anti-CD19 CAR using co-transduction as disclosed herein.

#### Example 6: Manufacturing CART Cells Using the Activated Rapid Manufacturing (ARM) Process

The ARM process of CART cells initiates with the preparation of the media as outlined in Table 25.

Cryopreserved leukapheresis product is used as the starting material and is processed for T cell enrichment. When available, the apheresis paperwork is utilized to define the T cell percentage. In the absence of the T cell percentage data on the apheresis paperwork, the sentinel vial testing is performed on incoming cryopreserved leukapheresis prod-

ucts to obtain T cell percentage target for the apheresis. The results for the T cell percentage determine how many bags are thawed on Day 0 of the ARM process.

20 Cryopreserved leukapheresis is thawed, washed, and then undergoes T cell selection and enrichment using Clinimacs® microbead technology. Viable nucleated cells (VNCs) are activated with TransACT (Miltenyi) and transduced with a lentiviral vector encoding the CAR. The viable cells selected with the Miltenyi microbeads are seeded into the centricult on the Prodigy®, which is a non-humidified incubation chamber. While in culture, the cells are suspended in Rapid media, which is an OptiMizer™ CTSTM based medium that contains the CTSTM Supplement (ThermoFisher), Glutamax, IL-2 and 2% Immune cell serum replacement amongst its components to promote T cell activation and transduction. Lentiviral transduction is performed once on the day of seeding after the TransACT has been added to the diluted cells in the culture media. Lentiviral vector will be thawed immediately prior to use on day 0 of seeding for up to 30 minutes at room temperature.

From the start of the process on Day 0 to the initiation of the culture wash and harvest, CART cells are cultured for 20-28 hours from seeding. Following culture, the cell suspension undergoes two culture washes and one harvest wash within the centricult chamber (Miltenyi Biotech).

After the harvest wash on the Clinimacs® Prodigy® on day 1, the cell suspension is sampled to determine viable cell count and viability. Cell suspension is then transferred to a centrifuge to be pelleted manually. The supernatant is removed, and the cell pellet is re-suspended in CS10 (Biologics Life Solution), resulting in a product formulation with a final DMSO concentration of ~10.0%. The viable cell count is formulated at the end of harvest for dosing. The doses are then distributed into individual cryobags and analytical sampling into cryovials.

Cryopreserved products are stored in monitored LN2 storage tanks, in a secure, limited access area until final release and shipping.

In some embodiments, the CART cells express dual CARs disclosed herein, e.g., anti-BCMA/anti-CD19 dual CARs disclosed herein. In some embodiments, the CART cells express a diabody CAR disclosed herein, e.g., an anti-BCMA/anti-CD19 diabody CAR disclosed herein. In some embodiments, the CART cells are engineered to express an anti-BCMA CAR and an anti-CD19 CAR using co-transduction as disclosed herein.

#### Example 7: Manufacture of CART Cells Expressing an Anti-BCMA CAR and an Anti-CD19 CAR

The rapid manufacturing process of CART cells begins with the preparation of the media as outlined in Table 33.

TABLE 33

Media type and point of use during CART manufacturing		
Media/Buffer Type	Composition	Process Step
Rapid Media (RM)	OpTmizer CTS CTS supplement ICSR GlutaMAX Reconstituted IL-2	Cell Seeding and activation
Rapid Buffer (RB)	CliniMACs Buffer (PBS with EDTA) HSA	Cell Wash and T cell enrichment
Culture/Harvest Wash Solution	PBS (no Mg/Ca and EDTA) HSA	Harvest Wash procedure
CryoMedia	CryoStor® (CS10) with DMSO	Harvest Formulation

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Cryopreserved leukapheresis is thawed. The thawed cells are diluted with the Rapid Buffer (Table 33) and washed on the CliniMACS® Prodigy® device. The T cells are selected by CliniMACS® CD4 and CD8 microbeads. Once the program is finished for T cell selection (approximately 3 h 40 min to 4 h 40 min), the reapplication bag will contain the cells suspended in Rapid Buffer (Table 33). A sample is taken for viability and cell count. The cell count and viability data from the positive fraction bag is used to determine the cell concentration when seeding the culture vessel for activation and vector transduction.

Following positive selection of T cells via the CliniMACS® microbeads (CD4 and CD8), the cells are seeded in the culture vessel, CentriCult in the Prodigy®, at a target of  $4.0 \times 10^8$ - $1.0 \times 10^9$  total viable cells at a targeted concentration of about  $4.0 \times 10^6$  viable cells/mL. Once the cells are seeded, the activation reagent (TransAct) is then added to the culture vessel.

The cells are then transduced with a lentiviral vector encoding an anti-BCMA CAR and a lentiviral vector encoding an anti-CD19 CAR. The vector volume to be used for transduction of T cells, following positive selection, is calculated based on a target Multiplicity of Infection (MOI) of 4.75 for the BCMA CAR lentiviral vector and a target MOI of 0.5 for the CD19 CAR lentiviral vector.

After a target of 24 hours (operating range 20-28 hours) of incubation at a temperature of 37° C. with nominal 5% CO<sub>2</sub>, the cells are processed for harvest wash.

Following the incubation, the cells are washed with Harvest Wash Solution (Table 33) three times to remove any non-integrated vector and residual viral particles, as well as any other process related impurities. Then, the cells are eluted and a sample for cell count and viability is taken for testing and the results are used to determine the volume required to re-suspend the cells for final formulation with CryoStor® CS10. The cells are then centrifuged to remove the Harvest Wash Solution and proceed with cryopreservation.

#### Example 8: Gene Signature Analysis of CART Cells Manufactured Using the ARM Process

#### Methods

##### Single Cell RNAseq

Single cell RNAseq libraries were generated using the 10x Genomics Chromium Controller instrument and supporting library construction kits.

Cryopreserved cells were thawed, counted and flow sorted (if required for study question), prior to being loaded on a 10x Genomics Instrument. Individual cells were loaded into droplets and RNA within individual droplets was bar-

coded via a GemCode bead. Barcoded RNA was released from droplets and converted into a whole transcriptome Illumina compatible sequencing library.

Generated libraries were sequenced on an Illumina HiSeq Instrument and analyzed using 10x Genomics analysis pipeline and Loupe Cell Browser software.

##### Single Cell Immune Cell Profiling

Whole transcriptome 10x Genomics single cell libraries were used as a template material to generate immune cell profiling and repertoire analysis. T cell receptor sequences were PCR amplified from Chromium Single Cell 5' Libraries and analyzed on an Illumina sequencing instrument.

##### Analysis Pipeline

Single cell RNAseq data was processed through the Cell Ranger analysis pipeline starting with FASTQ files. A detailed description of the Cell Ranger analysis pipeline can be found at: support.10xgenomics.com/single-cell-gene-expression/software/pipelines/latest/what-is-cell-ranger. The general pipeline included alignment, filtering, barcode counting, and UMI counting. Cellular barcodes were used to generate gene-barcode matrices, determine clusters, and perform gene expression analysis. Gene expression count data was normalized using the Seurat Bioconductor package. Cells were discarded from the analysis that had less than 200 expressed genes. Genes were discarded from the analysis that were only expressed in 2 cells or less. The remaining data was normalized with the Seurat log normalization method using a scale factor of 10,000. Data was scaled by regressing on the number of detected molecules per cell. The gene set score (GeneSetScore) was calculated by taking the mean log normalized gene expression value of all the genes in the gene set. Each gene is z-score normalized so that the mean expression of the gene across samples is 0 and standard deviation is 1. The gene set score is then calculated as the mean of the normalized values of the genes in the gene set. An exemplary gene set score calculation is described below.

For this example of gene set score calculation, the normalized gene expression of two (2) samples for six (6) genes is provided in Table 23. For the purposes of this exemplary calculation, the gene set consists of genes 1-4. Therefore, Sample 1 and 2 both have gene set scores of 0.

TABLE 23

Exemplary dataset for gene set score calculation		
	Sample 1	Sample 2
Gene 1	-3	0
Gene 2	3	0
Gene 3	1	0

TABLE 23-continued

Exemplary dataset for gene set score calculation		
	Sample 1	Sample 2
Gene 4	-1	0
Gene 5	10	4
Gene 6	-5	3

The gene set “Up TEM vs. Down TSCM” includes the following genes: MXRA7, CLIC1, NAT13, TBC1D2B, GLCCI1, DUSP10, APOBEC3D, CACNB3, ANXA2P2, TPRG1, EOMES, MATK, ARHGAP10, ADAM8, MAN1A1, SLFN12L, SH2D2A, EIF2C4, CD58, MYO1F, RAB27B, ERN1, NPC1, NBEAL2, APOBEC3G, SYTL2, SLC4A4, PIK3AP1, PTGDR, MAF, PLEKHA5, ADRB2, PLXND1, GNAO1, THBS1, PPP2R2B, CYTH3, KLRF1, FLJ16686, AUTS2, PTPRM, GNLY, and GFPT2.

The gene set “Up Treg vs. Down Teff” includes the following genes: C12orf75, SELPLG, SWAP70, RGS1, PRR11, SPATS2L, SPATS2L, TSHR, C14orf145, CASP8, SYT11, ACTN4, ANXA5, GLRX, HLA-DMB, PMCH, RAB11FIP1, IL32, FAM160B1, SHMT2, FRMD4B, CCR3, TNFRSF13B, NTNG2, CLDND1, BARD1, FCER1G, TYMS, ATP1B1, GJB6, FGL2, TK1, SLC2A8, CDKN2A, SKAP2, GPR55, CDCA7, S100A4, GDPD5, PMAIP1, ACOT9, CEP55, SGMS1, ADPRH, AKAP2, HDAC9, IKZF4, CARD17, VAV3, OBFC2A, ITGB1, CIITA, SETD7, HLA-DMA, CCR10, KIAA0101, SLC14A1, PTTG3P, DUSP10, FAM164A, PYHINI, MYO1F, SLC1A4, MYBL2, PTTG1, RRM2, TP53INP1, CCR5, ST8SIA6, TOX, BFSP2, ITPR1PL1, NCAPH, HLA-DPB2, SYT4, NINJ2, FAM46C, CCR4, GBP5, C15orf53, LMCD1, MK167, NUSAP1, PDE4A, E2F2, CD58, ARHGEF12, LOC100188949, FAS, HLA-DPB1, SELP, WEE1, HLA-DPA1, FCRL1, ICA1, CNTNAP1, OAS1, METTL7A, CCR6, HLA-DRB4, ANXA2P3, STAM, HLA-DQB2, LGALS1, ANXA2, P116, DUSP4, LAYN, ANXA2P2, PTPLA, ANXA2P1, ZNF365, LAIR2, LOC541471, RAS-GRP4, BCAS1, UTS2, MIAT, PRDM1, SEMA3G, FAM129A, HPGD, NCF4, LGALS3, CEACAM4, JAK-MIP1, TIGIT, HLA-DRA, IKZF2, HLA-DRB1, FANK1, RTKN2, TRIB1, FCRL3, and FOXP3.

The gene set “Down stemness” includes the following genes: ACE, BATF, CDK6, CHD2, ERCC2, HOXB4, MEOX1, SFRP1, SP7, SRF, TAL1, and XRCC5.

The gene set “Up hypoxia” includes the following genes: ABCB1, ACAT1, ADM, ADORA2B, AK2, AK3, ALDH1A1, ALDH1A3, ALDOA, ALDOC, ANGPT2, ANGPTL4, ANXA1, ANXA2, ANXA5, ARHGAP5, ARSE, ART1, BACE2, BATF3, BCL2L1, BCL2L2, BHLHE40, BHLHE41, BIK, BIRC2, BNIP3, BNIP3L, BPI, BTG1, C11orf2, C7orf68, CA12, CA9, CALD1, CCNG2, CCT6A, CD99, CDK1, CDKN1A, CDKN1B, CITED2, CLK1, CNOT7, COL4A5, COL5A1, COL5A2, COL5A3, CP, CTSD, CXCR4, D4S234E, DDT3, DDT4, 1-Dec, DKC1, DR1, EDN1, EDN2, EFNA1, EGF, EGR1, EIF4A3, ELF3, ELL2, ENG, ENO1, ENO3, ENPEP, EPO, ERRFI1, ETS1, F3, FABP5, FGF3, FKBP4, FLT1, FN1, FOS, FTL, GAPDH, GBE1, GLRX, GPI, GPRC5A, HAPI, HBP1, HDAC1, HDAC9, HERC3, HERPUD1, HGF, HIF1A, HK1, HK2, HLA-DQB1, HMOX1, HMOX2, HSPA5, HSPD1, HSPH1, HYOU1, ICAM1, ID2, IFI27, IGF2, IGFBP1, IGFBP2, IGFBP3, IGFBP5, IL6, IL8, INSIG1, IRF6, ITGA5, JUN, KDR, KRT14, KRT18, KRT19, LDHA, LDHB, LEP, LGALS1, LONP1, LOX, LRP1, MAP4, MET, MIF, MMP13, MMP2, MMP7, MPI, MT1L, MTL3P,

MUC1, MXI1, NDRG1, NFI1, NFKB1, NFKB2, NOS1, NOS2, NOS2P1, NOS2P2, NOS3, NR3C1, NR4A1, NT5E, ODC1, P4HA1, P4HA2, PAICS, PDGFB, PDK3, PFKFB1, PFKFB3, PFKFB4, PFKL, PGAM1, PGF, PGK1, PGK2, PGM1, PIM1, PIM2, PKM2, PLAUR, PLIN2, PLOD2, PNN, PNP, POLM, PPARA, PPAT, PROK1, PSMA3, PSMD9, PTGS1, PTGS2, QSOX1, RBPJ, RELA, RIOK3, RNASEL, RPL36A, RRP9, SAT1, SERPINB2, SERPINE1, SGSM2, SIAH2, SIN3A, SIRPA, SLC16A1, SLC16A2, SLC20A1, SLC2A1, SLC2A3, SLC3A2, SLC6A10P, SLC6A16, SLC6A6, SLC6A8, SORL1, SPP1, SRSF6, SSSCA1, STC2, STRA13, SYT7, TBPL1, TCEAL1, TEK, TF, TFF3, TFRC, TGFA, TGFB1, TGFB3, TGFB1I, TGM2, TH, THBS1, THBS2, TIMM17A, TNFAIP3, TP53, TPBG, TPD52, TPI1, TXN, TXNIP, UMPS, VEGFA, VEGFB, VEGFC, VIM, VPS11, and XRCC6.

The gene set “Up autophagy” includes the following genes: ABL1, ACBD5, ACIN1, ACTRT1, ADAMTS7, AKR1E2, ALKBH5, ALPK1, AMBRA1, ANXA5, ANXA7, ARSB, ASB2, ATG10, ATG12, ATG13, ATG14, ATG16L1, ATG16L2, ATG2A, ATG2B, ATG3, ATG4A, ATG4B, ATG4C, ATG4D, ATG5, ATG7, ATG9A, ATG9B, ATP13A2, ATP1B1, ATPAF1-AS1, ATPIF1, BECN1, BECN1P1, BLOC1S1, BMP2KL, BNIP1, BNIP3, BOC, C11orf2, C11orf41, C12orf44, C12orf5, C14orf133, C1orf210, C5, C6orf106, C7orf59, C7orf68, C8orf59, C9orf72, CA7, CALCB, CALCOCO2, CAPS, CCDC36, CD163L1, CD93, CDC37, CDKN2A, CHAF1B, CHMP2A, CHMP2B, CHMP3, CHMP4A, CHMP4B, CHMP4C, CHMP6, CHST3, CISD2, CLDN7, CLEC16A, CLN3, CLVS1, COX8A, CPA3, CRNL1, CSPG5, CTSA, CTSB, CTSD, CXCR7, DAP, DKKL1, DNAAF2, DPF3, DRAM1, DRAM2, DYNLL1, DYNLL2, DZANK1, EI24, EIF2S1, EPG5, EPM2A, FABP1, FAM125A, FAM131B, FAM134B, FAM13B, FAM176A, FAM176B, FAM48A, FANCC, FANCF, FANCL, FBXO7, FCGR3B, FGF14, FGF7, FGFBP1, FIS1, FNBP1L, FOXO1, FUNDC1, FUNDC2, FXR2, GABARAP, GABARAP1, GABARAP2, GABA-RAPL3, GABRA5, GDF5, GMIP, HAPI, HAPLN1, HBXIP, HCAR1, HDAC6, HGS, HIST1H3A, HIST1H3B, HIST1H3C, HIST1H3D, HIST1H3E, HIST1H3F, HIST1H3G, HIST1H3H, HIST1H3I, HIST1H3J, HK2, HMGBl, HPR, HSF2BP, HSP90AA1, HSPA8, IFI16, IPPK, IRGM, IST1, ITGB4, ITPKC, KCNK3, KCNQ1, KIAA0226, KIAA1324, KRCC1, KRT15, KRT73, LAMPI, LAMP2, LAMTOR1, LAMTOR2, LAMTOR3, LARP1B, LENG9, LGALS8, LIX1, LIX1L, LMCD1, LRRK2, LRSAM1, LSM4, MAP1A, MAP1LC3A, MAP1LC3B, MAP1LC3B2, MAP1LC3C, MAP1S, MAP2K1, MAP3K12, MARK2, MBD5, MDH1, MEX3C, MFN1, MFN2, MLST8, MRPS10, MRPS2, MSTN, MTERFD1, MTMR14, MTMR3, MTOR, MTSS1, MYH11, MYLK, MYOM1, NBR1, NDUFB9, NEFM, NHLRC1, NME2, NPC1, NR2C2, NRBF2, NTHL1, NUP93, OBSCN, OPTN, P2RX5, PACS2, PARK2, PARK7, PDK1, PDK4, PEX13, PEX3, PFKP, PGK2, PHF23, PHYHIP, PI4K2A, PIK3C3, PIK3CA, PIK3CB, PIK3R4, PINK1, PLEKHM1, PLOD2, PNPO, PPARGC1A, PPY, PRKAA1, PRKAA2, PRKAB1, PRKAB2, PRKAG1, PRKAG2, PRKAG3, PRKD2, PRKG1, PSEN1, PTPN22, RAB12, RAB1A, RAB1B, RAB23, RAB24, RAB33B, RAB39, RAB7A, RB1CC1, RBM18, REEP2, REP15, RFWD3, RGS19, RHEB, RIMS3, RNF185, RNF41, RPS27A, RPTOR, RRAGA, RRAGB, RRAGC, RRAGD, S100A8, S100A9, SCN1A, SERPINB10, SESN2, SFRP4, SH3GLB1, SIRT2, SLC1A3, SLC1A4, SLC22A3, SLC25A19, SLC35B3, SLC35C1,

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SLC37A4, SLC6A1, SLCO1A2, SMURF1, SNAP29, SNA-PIN, SNF8, SNRPB, SNRPB2, SNRPD1, SNRPF, SNTG1, SNX14, SPATA18, SQSTM1, SRPX, STAM, STAM2, STAT2, STBD1, STK11, STK32A, STOM, STX12, STX17, SUPT3H, TBC1D17, TBC1D25, TBC1D5, TCIRG1, TEAD4, TECPR1, TECPR2, TFEB, TM9SF1, TMBIM6, TMEM203, TMEM208, TMEM39A, TMEM39B, TMEM59, TMEM74, TMEM93, TNK, TOLLIP, TOMM20, TOMM22, TOMM40, TOMM5, TOMM6, TOMM7, TOMM70A, TP53INP1, TP53INP2, TRAPP8, TREM1, TRIM17, TRIMS, TSG101, TXLNA, UBA52, UBB, UBC, UBQLN1, UBQLN2, UBQLN4, ULK1, ULK2, ULK3, USP10, USP13, USP30, UVRAG, VAMP7, VAMP8, VDAC1, VMP1, VPS11, VPS16, VPS18, VPS25, VPS28, VPS33A, VPS33B, VPS36, VPS37A, VPS37B, VPS37C, VPS37D, VPS39, VPS41, VPS4A, VPS4B, VTA1, VTI1A, VTI1B, WDFY3, WDR45, WDR45L, WIP1I, WIP12, XBP1, YIPF1, ZCCHC17, ZFYVE1, ZKSCAN3, ZNF189, ZNF593, and ZNF681.

The gene set “Up resting vs. Down activated” includes the following genes: ABCA7, ABCF3, ACAP2, AMT, ANKH, ATF7IP2, ATG14, ATP1A1, ATXN7, ATXN7L3B, BCL7A, BEX4, BSDC1, BTG1, BTG2, BTN3A1, C11orf21, C19orf22, C21orf2, CAMK2G, CARS2, CCNL2, CD248, CD5, CD55, CEP164, CHKB, CLK1, CLK4, CTSL1, DBP, DCUN1D2, DENND1C, DGKD, DLG1, DUSP1, EAPP, ECE1, ECHDC2, ERBB2IP, FAM117A, FAM134B, FAM134C, FAM169A, FAM190B, FAU, FLJ10038, FOXJ2, FOXJ3, FOXL1, FOXO1, FXYD5, FYB, HLA-E, HSPA1L, HYAL2, ICAM2, IFIT5, IFITM1, IKBKB, IQSEC1, IRS4, KIAA0664L3, KIAA0748, KLF3, KLF9, KRT18, LEF1, LINC00342, LIPA, LIPT1, LLGL2, LMBR1L, LPAR2, LTBP3, LYPD3, LZTFL1, MANBA, MAP2K6, MAP3K1, MARCH8, MAU2, MGEA5, MMP8, MPO, MSL1, MSL3, MYH3, MYLIP, NAGPA, NDST2, NISCH, NKTR, NLRP1, NOSIP, NPIP, NUMA1, PAIP2B, PAPD7, PBXIP1, PCIF1, PI4KA, PLCL2, PLEKHA1, PLEKHF2, PNISR, PPFBP2, PRKCA, PRKCZ, PRKD3, PRMT2, PTP4A3, PXX, RASA2, RASA3, RASGRP2, RBM38, REPIN1, RNF38, RNF44, ROR1, RPL30, RPL32, RPLP1, RPS20, RPS24, RPS27, RPS6, RPS9, RXRA, RYK, SCAND2, SEMA4C, SETD1B, SETD6, SETX, SF3B1, SH2B1, SLC2A4RG, SLC35E2B, SLC46A3, SMAGP, SMARCE1, SMPD1, SNPH, SP140L, SPATA6, SPG7, SREK1IP1, SRSF5, STAT5B, SVIL, SYF2, SYNJ2BP, TAF1C, TBC1D4, TCF20, TECTA, TES, TMEM127, TMEM159, TMEM30B, TMEM66, TMEM8B, TP53TG1, TPCN1, TRIM22, TRIM44, TSC1, TSC22D1, TSC22D3, TSPYL2, TTC9, TTN, UBE2G2, USP33, USP34, VAMP1, VILL, VIPR1, VPS13C, ZBED5, ZBTB25, ZBTB40, ZC3H3, ZFP161, ZFP36L1, ZFP36L2, ZHX2, ZMYM5, ZNF136, ZNF148, ZNF318, ZNF350, ZNF512B, ZNF609, ZNF652, ZNF83, ZNF862, and ZNF91.

The gene set “Progressively up in memory differentiation” includes the following genes: MTCH2, RAB6C, KIAA0195, SETD2, C2orf24, NRD1, GNA13, COPA, SELT, TNIP1, CBFA2T2, LRP10, PRKCI, BRE, ANKS1A, PNPLA6, ARL6IP1, WDFY1, MAPK1, GPR153, SHKBP1, MAP1LC3B2, PIP4K2A, HCN3, GTPBP1, TLN1, C4orf34, KIF3B, TCIRG1, PPP3CA, ATG4D, TYMP, TRAF6, C17orf76, WIFP1, FAM108A1, MYL6, NRM, SPCS2, GGT3P, GALKI, CLIP4, ARL4C, YWHAQ, LPCAT4, ATG2A, IDS, TBC1D5, DMPK, ST6GALNAC6, REEP5, ABHD6, KIAA0247, EMB, TSEN54, SPIRE2, PIWL4, ZSCAN22, ICAM1, CHD9, LPIN2, SETD8, ZC3H12A, ULBP3, IL15RA, HLA-DQB2, LCP1, CHP, RUNX3,

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TMEM43, REEP4, MEF2D, ABL1, TMEM39A, PCBp4, PLCD1, CHST12, RASGRP1, C1orf58, C11orf63, C6orf129, FHOD1, DKFZp434F142, PIK3CG, ITPR3, BTG3, C4orf50, CNNM3, IFI16, AK1, CDK2AP1, REL, BCL2L1, MVD, TTC39C, PLEKHA2, FKBP11, EML4, FANCA, CDCA4, FUCA2, MFSD10, TBCD, CAPN2, IQGAP1, CHST11, PIK3R1, MYOSA, KIR2DL3, DLG3, MXD4, RALGD5, S1PR5, WSB2, CCR3, TIPARP, SP140, CD151, SOX13, KRTAP5-2, NF1, PEA15, PARP8, RNF166, UEVLD, LIMK1, CACNB1, TMX4, SLC6A6, LBA1, SV2A, LLGL2, IRF1, PPP2R5C, CD99, RAPGEF1, PPP4R1, OSBPL7, FOXP4, SLA2, TBC1D2B, ST7, JAZF1, GGA2, PI4K2A, CD68, LPGAT1, STX11, ZAK, FAM160B1, RORA, C8orf80, APOBEC3F, TGFB1, DNAJC1, GPR114, LRP8, CD69, CMIP, NAT13, TGFB1, FLJ00049, ANTXR2, NR4A3, IL12RB1, NTNG2, RDX, MLLT4, GPRIN3, ADCY9, CD300A, SCD5, ABI3, PTPN22, LGALS1, SYTL3, BMPR1A, TBK1, PMAIP1, RASGEF1A, GCNT1, GABARAPL1, STOM, CALHM2, ABCA2, PPP1R16B, SYNE2, PAM, C12orf75, CLCF1, MXRA7, APOBEC3C, CLSTN3, ACOT9, HIP1, LAG3, TNFAIP3, DCBLD1, KLF6, CACNB3, RNF19A, RAB27A, FADS3, DLG5, APOBEC3D, TNFRSF1B, ACTN4, TBKBP1, ATXN1, ARAP2, ARHGEL12, FAM53B, MAN1A1, FAM38A, PLXNC1, GRLF1, SRGN, HLA-DRB5, B4GALT5, WIP1I, PTPRJ, SLFN11, DUSP2, ANXA5, AHNAK, NEO1, CLIC1, EIF2C4, MAP3K5, IL2RB, PLEKHG1, MYO6, GTDC1, EDARADD, GALM, TARP, ADAM8, MSC, HNRPLL, SYT11, ATP2B4, NHSL2, MATK, ARHGAP18, SLFN12L, SPATS2L, RAB27B, PIK3R3, TP53INP1, MBOAT1, GYG1, KATNAL1, FAM46C, ZC3HAV1L, ANXA2P2, CTNNA1, NPC1, C3AR1, CRIM1, SH2D2A, ERN1, YPEL1, TBX21, SLC1A4, FASLG, PHACTR2, GALNT3, ADRB2, PIK3AP1, TLR3, PLEKHA5, DUSP10, GNAO1, PTGDR, FRMD4B, ANXA2, EOMES, CADM1, MAF, TPRG1, NBEAL2, PPP2R2B, PELO, SLC4A4, KLRF1, FOSL2, RGS2, TGFBR3, PRF1, MYO1F, GAB3, C17orf66, MICAL2, CYTH3, TOX, HLA-DRA, SYNE1, WEE1, PYHINI, F2R, PLD1, THBS1, CD58, FAS, NETO2, CXCR6, ST6GALNAC2, DUSP4, AUTS2, C1orf21, KLRL1, TNIP3, GZMA, PRR5L, PRDM1, ST8SIA6, PLXND1, PTPRM, GFPT2, MYBL1, SLAMF7, FLJ16686, GNLY, ZEB2, CST7, ILI8RAP, CCL5, KLRD1, and KLRB1.

The gene set “Up TEM vs. Down TN” includes the following genes: MYOSA, MXD4, STK3, S1PR5, GLCCI1, CCR3, SOX13, KRTAP5-2, PEA15, PARP8, RNF166, UEVLD, LIMK1, SLC6A6, SV2A, KPNA2, OSBPL7, ST7, GGA2, PI4K2A, CD68, ZAK, RORA, TGFB1, DNAJC1, JOSD1, ZFYVE28, LRP8, OSBPL3, CMIP, NAT13, TGFB1, ANTXR2, NR4A3, RDX, ADCY9, CHN1, CD300A, SCD5, PTPN22, LGALS1, RASGEF1A, GCNT1, GLUL, ABCA2, CLDND1, PAM, CLCF1, MXRA7, CLSTN3, ACOT9, METRNL, BMPR1A, LRIG1, APOBEC3G, CACNB3, RNF19A, RAB27A, FADS3, ACTN4, TBKBP1, FAM53B, MAN1A1, FAM38A, GRLF1, B4GALT5, WIP1I, DUSP2, ANXA5, AHNAK, CLIC1, MAP3K5, ST8SIA1, TARP, ADAM8, MATK, SLFN12L, PIK3R3, FAM46C, ANXA2P2, CTNNA1, NPC1, SH2D2A, ERN1, YPEL1, TBX21, STOM, PHACTR2, GBP5, ADRB2, PIK3AP1, DUSP10, PTGDR, EOMES, MAF, TPRG1, NBEAL2, NCAPH, SLC4A4, FOSL2, RGS2, TGFBR3, MYO1F, C17orf66, CYTH3, WEE1, PYHINI, F2R, THBS1, CD58, AUTS2, FAM129A,

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TNIP3, GZMA, PRR5L, PRDM1, PLXND1, PTprm, GFPT2, MYBL1, SLAMF7, ZEB2, CST7, CCL5, GZMK, and KLKB1.

Other gene sets describing similar processes and/or characteristics can also be used to characterize cell phenotypes described above.

Cell Ranger VDJ was used to generate single cell VDJ sequences and annotations for each single cell 5' library. Loupe Cell Browser software and Bioconductor packages were used for data analysis and visualization.

## Results

This example aims to compare T cell states between purified T cells which served as input cells, CART cells manufactured using the ARM process (labeled as "Day 1" cells), and CART cells manufactured using the TM process (labeled as "Day 9" cells) using single-cell RNA-seq (scRNA-seq). In addition, single-cell TCR-seq (scTCR-seq) was performed to study clonality and track cell differentiation from input to post-manufacturing materials.

As shown in FIGS. 23A-23C, input cells had the fewest expressed genes and UMIs, suggesting these cells were not transcriptionally active and were in a resting state. Day 1 and Day 9 cells were expressing more genes, with Day 9 cells being the most transcriptionally active. Similar results are shown in FIGS. 24A-24D. Input cells were not expressing proliferation genes (FIGS. 24A and 24D).

Additional gene set analysis data are shown in FIGS. 25A-25E. Different populations of cells were compared using the median gene set scores. Day 1 cells and input cells were in a younger, more stem-like memory state (FIGS. 25A-25C). In FIG. 25A, the median GeneSetScore (Up TEM vs. Down TSCM) values for Day 1 cells, Day 9 cells, and input cells are -0.084, 0.035, and -0.1, respectively. In FIG. 25B, the median GeneSetScore (Up Treg vs. Down Teff) values for Day 1 cells, Day 9 cells, and input cells are -0.082, 0.087, and -0.071, respectively. In FIG. 25C, the median GeneSetScore (Down stemness) values for Day 1 cells, Day 9 cells, and input cells are -0.062, 0.14, and -0.081, respectively.

In addition, Day 1 cells were in a more ideal metabolic state compared to Day 9 cells (FIGS. 25D and 25E). In FIG. 25D, the median GeneSetScore (Up hypoxia) values for Day 1 cells, Day 9 cells, and input cells are 0.019, 0.11, and -0.096, respectively. In FIG. 25E, the median GeneSetScore (Up autophagy) values for Day 1 cells, Day 9 cells, and input cells are 0.066, 0.11, and -0.09, respectively.

Based on gene expression, the input cells contain four clusters. Cluster 0 is characterized by high expression of LMNA, S100A4, etc. Cluster 1 is characterized by high expression of RP913, PRKCQ-AS1, etc. Cluster 2 is characterized by high expression of PR11-291B21.2, CD8B, etc. Cluster 3 is characterized by high expression of NKG7, GZMH, CCL5, CST7, GNLY, FGFBP2, GZMA, CCL4, CTSW, CD8A, etc. In a T-Distributed Stochastic Neighbor Embedding (TSNE) plot for the input cells, Cluster 3 stood out from the other cells, and Cluster 1 and Cluster 2 were hard to differentiate.

According to the gene set analysis shown in FIGS. 26A-26C, Cluster 0 and Cluster 3 were enriched for a T regulatory phenotype compared to Cluster 1 and Cluster 2 which were enriched for a T effector phenotype. Cluster 3 was dominated by late memory/effector memory (TEM) cells, Cluster 1 and Cluster 2 were early memory and naïve cells, and Cluster 0 is in the middle. The majority of the input cells were in an early memory, naïve state. Without wishing to be bound by theory, these cells may do the best during the manufacturing procedure.

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Less transcriptional heterogeneity was seen in Day 1 cells and Day 9 cells (data not shown).

Like the input population, Day 1 cells showed a large cluster of early memory cells and a smaller cluster of late memory cells in a TSNE plot. Similar to what was seen with Cluster 3 of the input cells. In contrast, Day 9 cells did not show distinct clusters of early memory cells in a TSNE plot. This implies that by day 9, the cells had become more homogeneous.

TCRs were sequenced and clonotype diversity was measured. Overall, the three clonotype profiles were very flat—most clones were only picked up once (FIGS. 27A-27C and Table 24). Shannon entropy in Table 24 measures the flatness of the distribution. The dominant clones in the input cells were late memory cells. Day 1 cells looked similar to the input cells but started to even out. By day 9, the dominate clones had substantially evened out and the distribution was much more flat. The diversity measurement was the highest at day 9 because there was a much more even and flat distribution in Day 9 cells than in the input cells or Day 1 cells.

TABLE 24

	Measurements of TCR diversity		
	Input	Day 1 product	Day 9 product
Average clones per clonotype	1.10	1.05	1.07
Estimated number of cells	7344	7687	7233
Total number of clonotypes	5325	7403	6736
Diversity	342.27	802.94	3382.62
Normalized Shannon entropy	9.98E-01	9.95E-01	9.96E-01

## Summary

There were significant T cell state differences between Day 1 and Day 9 products. Day 1 cells were much more similar to input cells and had enrichment for stemness signatures, indicating a more efficacious product.

## Example 9: Co-Transduction of BCMA CAR and CD19 CAR, Evaluation of MOI, and Efficacy Studies

This example describes characterization of CART cells generated by co-transducing T cells with a lentiviral vector encoding a BCMA CAR and a lentiviral vector encoding a CD19 CAR. The BCMA CAR comprises the amino acid sequence of SEQ ID NO: 107 and the CD19 CAR comprises the amino acid sequence of SEQ ID NO: 225.

## Cell Preparation and CAR Transduction

Four different MOI combinations of BCMA and CD19 CAR in transducing T cells were tested in a 24-well plate format. The BCMA CAR lentiviral vector and CD19 CAR lentiviral vector were used at MOIs of 5 and 1, respectively (5/1 in FIGS. 28A and 28B); 5 and 0.5, respectively (5/0.5 in FIGS. 28A and 28B); 2.5 and 1, respectively (2.5/1 in FIGS. 28A and 28B); or 2.5 and 0.5, respectively (2.5/0.5 in FIGS. 28A and 28B). T cells purified by Prodigy were seeded at 3e<sup>6</sup>/mL, 1 mL/well into 24-well plates and both BCMA and CD19 CAR vectors were added at different MOIs as indicated above. Upon seeding, TransAct (Miltenyi Biotec), a polymeric nanomatrix conjugated to anti-CD3 and anti-CD28 agonist, was added. Cells were incubated in OptiMizer complete T cell media containing 100 IU/mL

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human recombinant IL-2 (Prometheus, San Diego, CA) and 2% ICRS (Life Technologies) at 37° C. and 5% CO<sub>2</sub> for 24 hours prior to harvest.

Cells were then washed three times with 3x volume of PBS+1% HAS. After cultivation and harvest wash, viability and cell count were assessed to determine the impact of vector titration on the final product.

Cells were then re-cultured at 1×10<sup>6</sup> VNC/mL in a 24-well plate and incubated for 6 additional days. FACS analysis to assess anti-BCMA CAR expression was performed at days 4 and 7 post-transduction (3 and 6 days post-harvest).

#### CAR Expression Analysis

Samples were measured on a flow cytometer (BD LSR-Fortessa), and data were analyzed with FlowJo software. With ARM process, as CAR may not be fully integrated and expressed ex vivo within 24h, 96 h post viral addition could serve as a surrogate time point for in vitro and in vivo dosing strategy when the CAR is being stably expressed. The same strategy was adopted for dual targeting cocktail CAR measurements.

FACS analyses indicated that co-transduction of BCMA and CD19 CAR in T cells resulted in three distinct CAR+ subpopulations, and their proportions vary at the tested four different MOI combinations (FIG. 28A), indicating a cocktail CAR-T product could be successfully generated by co-transduction of BCMA and CD19 CAR. At an MOI of 5/0.5, mono anti-BCMA CAR+(anti-CD19 CAR negative) was highest with 20.7%, followed by double+ CAR at 16.2% and mono anti-CD19 CAR+ at 10.5%. Total BCMA CAR+ calculated as double+ CAR % plus mono anti-BCMA CAR+ was 36.9%, while total CD19 CAR+ was 26.7% (FIGS. 28A and 28B). Both 2.5/0.5 and 2.5/1 MOI ratios resulted in much more mono CD19 CAR+% than double+ and mono anti-BCMA CAR+. Moreover, double+ CAR % is positively correlated with total MOI usage (FIG. 28B). Total CAR+% is similar between MOI 5/1 and MOI 5/0.5. CAR expression in each population was observed to be relatively stable from day 4 to day 7 post-transduction, including BCMA or CD19 CAR transduced T cells (FIGS. 28A and 28B). Data was consistent among three donors. In some embodiments, a MOI 4-5 of BCMA CAR and a MOI 0.5 of CD19 CAR for co-transduction are used to generate dual targeting cocktail CART product.

In addition, large-scale run experiments were conducted entirely on the Clinimacs Prodigy from T cell enrichment, T cell seeding, activation, transduction and cultivation, to harvest washes in CentriCult prior to formulation and cryopreservation. A MOI of 4/0.5 or 4.75/0.5 of BCMA/CD19CAR was used. This study used a seeding density of 3e<sup>6</sup>/mL in a total of 250 mL for 7.5e<sup>8</sup> total cells. The cells were harvested at 24 hr, washed 3x with PBS+1% HAS and cryopreserved for downstream application. The remaining T cells were collected to generate respective control groups as UTD, BCMACART and CD19CART. An aliquot was taken and re-cultured at 1e<sup>6</sup>/mL in a 24 well plate for flow cytometry analyses to assess BCMA-CAR expression at day 4 post-transduction.

FIG. 29 showed that dual targeting cocktail CART contained 11.8% of mono anti-BCMA CART cells, 4.31% of double CART cells and ~9% of mono anti-CD19 CART cells on day 4 post-transduction. In this study, total anti-BCMA CAR+% calculated as double CAR+% plus mono anti-BCMA CAR+% was 16%; while total anti-CD19 CAR+% calculated as double CAR+% plus mono anti-CD19 CAR+% was 13.4%.

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The dual cocktail CART in vivo activity was analyzed in three xenograft mouse models: 1) a KMS-11-luc model of multiple myeloma (this BCMA-expressing model is tagged with a luciferase reporter construct, which allows the disease to be monitored systemically in the bone marrow via bioluminescent imaging); 2) a mixed tumor model established by mixing 95% of KMS-11-luc myeloma cells with 5% of CD19+ tumors (e.g., Nalm-6-luc) to mimic heterogeneity of MM patients; and 3) a Nalm-6-luc model to evaluate the specificity of CD19 targeting and additional expansion of the double positive CART population of dual targeting cocktail CART. BCMACART and CD19CART served as controls for their respective models. For CAR-T cell dose calculation, the total anti-BCMA CAR+% was measured on day 4 post-transduction for models 1 and 2, while the total anti-CD19 CAR+% was measured on day 4 post-transduction for model 3. The UTD dose reflected the highest total T cell dose of the respective process.

The tumor regression curves for all the groups in the three models are shown in FIGS. 30A-E. In the KMS-11-luc model, both dual targeting cocktail CART and BCMACART induced tumor regression in a dose-dependent manner as shown in FIG. 30A. At 1e<sup>4</sup> dose, both dual targeting cocktail CART and BCMACART showed delayed tumor inhibition at similar pace, and both were able to clear tumor at the end of study. Dual targeting cocktail CART exhibited more effective tumor clearance than BCMACART at 5e<sup>4</sup> dose, in which dual targeting cocktail CART cleared tumor by day 14 post CAR-T infusion, while BCMACART showed at least one-week delayed effect. In a repeated study by using the remaining cell products from the same batch, covering a wider dose ranges (1e<sup>4</sup>, 5e<sup>4</sup>, 1.5e<sup>5</sup>) (FIG. 30B), dose dependency was confirmed in tumor regression by dual targeting cocktail CART. The regression curves of dual targeting cocktail CART at 1.5e<sup>5</sup>, 5e<sup>4</sup> and BCMACART at 1.5e<sup>5</sup> overlay. BCMACART at 5e<sup>4</sup> was able to eliminate tumor by day 14 post CAR-T infusion in this cohort of mice, despite a slightly slower tumor regression than dual targeting cocktail CART at the same dose over the course of 14 days post CAR-T infusion. At 1e<sup>4</sup> dose, dual targeting cocktail CART showed better efficacy than BCMACART. Briefly, using KMS-11-luc model, it was demonstrated that dual targeting cocktail CART was able to specifically target BCMA, shown to be as potent as BCMACART in killing BCMA+ multiple myeloma tumor, and was even more potent than BCMACART at lower doses.

Next, the efficacy of dual targeting cocktail CART was evaluated when both BCMA and CD19 were present in a “mixed” model, where KMS-11-luc cells mixed with 5% of Nam1-6-luc cells were implanted to mice. In the mixed tumor model as shown in FIG. 30C, only dual targeting cocktail CART at 5e<sup>4</sup> and 1e<sup>4</sup> demonstrated partial tumor inhibition in a dose dependent manner, while neither BCMACART nor CD19CART showed any effect at 5e<sup>4</sup> dose. In a repeated study covering a higher dose group as shown in FIG. 30D, it was demonstrated that dual targeting cocktail CART at 1.5e<sup>5</sup> was able to eliminate mixed tumors by day 14 post CAR-T infusion, and tumor suppression was dose dependent. In contrast, BCMACART and CD19CART at 1.5e<sup>5</sup> only showed partial tumor inhibition in this mixed model when both BCMA and CD19 were present.

Last, Nalm-6-luc model was used to show if dual targeting cocktail CART could specifically target CD19+ tumor. As indicated in FIG. 30E, dual targeting cocktail CART was also able to eliminate Nalm-6-luc tumors in a dose dependent manner comparable to monoCD19CART at a higher dose and better than monoCD19CART at a lower dose.

**357****Example 10: Evaluation of MOI for BCMA/CD19 CART Cellular Product Manufacturing**

Based on the qPCR titer, a titration of the BCMA-CAR virus was performed to determine the optimum vector ratio of BCMA-CAR/CD19-CAR. Briefly, the T cells were thawed and resuspended at a density of  $3 \times 10^6$  VNCs/mL or  $6 \times 10^6$  VNCs/mL. For each MOI tested, 1 mL of the cell suspension was plated in a 24-well plate, transduced at time 0, and incubated for 20-24 hours. Each 1 mL culture was then manually washed with  $3 \times 2$  mL of PBS+1% HSA. After cultivation and harvest wash, viability and cell count were assessed to determine the impact of the vector titration on final product. Harvested cells were then placed into culture at  $1 \times 10^6$  VNCs/mL and CAR (BCMA and CD19) expression were measured 72 hours and 144 hours post-harvest (Day 3 and Day 6 post-harvest (PH) (Day 4 and Day 7 post transduction) Table 34 and FIG. 31).

**TABLE 34**

Transduction of BCMA/CD19 dual CART cellular product GMP Vector Titration						
Donor ID	Day 0 seeding	MOI (TU/cell)	% CAR (Total BCMA-CAR = mono BCMA population + double BCMA/CD19 CAR population)			% mono CD19 CAR
			BCMA-CAR/	Day 3 PH	Day 6 PH	
Donor A	3e6	4/0.5	34.4	40.6	11.0	14.4
		5/0.5	38.3	49.1	8.9	12.1
	6e6	4/0.5	32.6	40.7	9.4	13.3
		5/0.5	38.1	47.8	8.7	11.7
Donor B	3e6	4/0.5	38.0	47.9	11.1	14.9
		5/0.5	40.6	52.9	9.7	12.6
	6e6	4/0.5	40.6	51.2	12.1	16.7
		5/0.5	43.0	55.9	9.9	13.6

In some embodiments, the total number of BCMA CAR+ viable T cells, measured by flow cytometry, 4 days post transduction (or 3 days post-harvest) is used for dose related calculations. In some embodiments, T cells are seeded at a density of about  $4 \times 10^6$  VNC/mL in CentriCult. In some embodiments, the BCMA CAR vector is used at a MOI of 4.75 and the CD19 CAR vector is used at a MOI of 0.5.

In a separate study, BCMA/CD19 CART cells were manufactured using the co-transduction rapid manufacturing approach described above at a large scale on an automated-closed system device, the CliniMACS Prodigy. Briefly, the process begins with the selection of T cells from a cryopreserved leukopak. T cells are positively selected using CD4 and CD8 microbeads. Post-selection, the T-cells are eluted into the reapplication bag and a sample is removed to assess cell concentration, viability and purity. T cells are then activated and transduced with a lentiviral vector encoding an anti-BCMA CAR and a lentiviral vector encoding an anti-CD19 CAR. As shown in FIG. 32, the T cell subsets from the output of the Prodigy did not differ from the input for the apheresis.

**Example 11: Further Characterization of T Cells Engineered to Express an Anti-BCMA CAR and an Anti-CD19 CAR**

This example describes further characterization of the BCMA/CD19 CART cellular product that was generated as

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described in Example 9. This cellular product contains three different CAR+ populations: mono anti-BCMA CAR-T cells, mono anti-CD19 CAR-T cells, and double-positive anti-BCMA/anti-CD19 CAR-T cells. In addition, this cellular product also contains a population of untransduced T cells.

**Plasma IFN- $\gamma$  in BCMA/CD19 Dual CART Cellular Product Treated Mice**

IFN- $\gamma$  is a hallmark of CAR-T cell activation in response to target engagement. The kinetics of plasma IFN- $\gamma$  was analyzed in the in vivo studies described in Example 9. As shown in FIGS. 33A and 33B, all CAR-T treated groups showed low levels of circulating IFN- $\gamma$  (10-50 pg/ml) at day 2 and continued increasing IFN- $\gamma$  secretion afterward.

**Non-Clinical Pharmacokinetics and Metabolism**

The expansion of the BCMA/CD19 dual CART cellular product in peripheral blood (including mono anti-BCMA, mono anti-CD19, or double-positive anti-BCMA/anti-CD19 CAR-T cells) was analyzed by flow cytometry up to 3 weeks after infusion, and compared to the benchmarked BCMA CART in the KMS-11-luc model. Both CD3+ T cell and CAR+ T cell expansion were observed in all CAR-T treatment groups. Dose-dependent cellular expansion was observed for the BCMA/CD19 dual CART cellular product in dual or mono CAR+ T cell populations. Based on data from two studies, the BCMA/CD19 dual CART cellular product showed slightly higher expansion of BCMA targeting CAR+ T cells and total CAR+ T cells as compared to BCMA CART.

Antigen dependent expansion of the BCMA/CD19 dual CART cellular product was demonstrated by assessing expansion of CAR+ T cells in three models (KMS-11, Nalm-6, and mixed). In the BCMA expressing KMS-11 xenograft model, double-positive anti-BCMA/anti-CD19 and mono anti-BCMA CAR+ T cells expanded extensively, while in CD19 expressing Nalm-6 xenograft model, double-positive anti-BCMA/anti-CD19 and mono anti-CD19 CAR+ T cells expanded extensively. The double-positive CAR-T cell population was able to expand with activation from either BCMA or CD19 antigen alone. The initial expansion rates of double-positive anti-BCMA/anti-CD19 and mono anti-BCMA CAR+ T cells were comparable in the KMS-11 model, as were those of the double-positive CAR and mono anti-CD19 CAR+ T cells in the Nalm-6 model.

**Conclusions**

The BCMA/CD19 dual CART cellular product is a novel anti-BCMA and anti-CD19 dual-targeting CAR-T cell product generated using a rapid manufacturing process, which preserves T-cell stemness.

In the three xenograft mice models (KMS-11, Nalm-6, and mixed), the BCMA/CD19 dual CART cellular product demonstrated potent in vivo pharmacology by controlling tumor growth, inducing CAR-T expansion and cytokine production, in an antigen-dependent and dose-dependent manner.

Tumor elimination in the mixed model was achieved by using the dual-targeting BCMA/CD19 CART cellular product, with increased tumor regression in a dose dependent fashion. Neither mono BCMA CART nor mono CD19 CART showed tumor regression in the mixed model. In addition, the BCMA/CD19 dual CART cellular product showed extended CAR-T expansion in vivo while the double-positive CAR population expanded with activation from either BCMA or CD19 alone. In the KMS-11-luc-model for multiple myeloma, the BCMA/CD19 dual CART cellular product showed improvement in tumor growth

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control at the higher dose levels tested and better tumor growth control at the lower dose level tested compared with BCMA CART.

These results support the BCMA/CD19 dual CART cellular product as a dual-targeting CAR-T that may change clinical outcomes by addressing the potential contribution of BCMA-/CD19+ stem/progenitor cells to multiple myeloma relapse, potentially providing deeper and more durable responses than traditionally manufactured or single antigen BCMA-targeting CAR-T.

**Example 12: Phase I Clinical Trial of Anti-BCMA CART Cells Manufactured Using the ARM Process**

This example describes an open-label, phase I study to assess the safety and tolerability of an anti-BCMA CART cell therapy that is manufactured using the ARM process in adult patients with relapsed and/or refractory multiple myeloma.

Primary outcome measures include: incidence and nature of Dose Limiting Toxicities (DLTs) during the first 28 days after anti-BCMA CAR-T cell administration, as well as incidence and severity of adverse events (AEs) and serious adverse events (SAEs), including changes in laboratory values, ECGs, and vital signs after anti-BCMA CAR-T cell administration.

Secondary outcome measures include: manufacture success rate (defined as number of subjects treated with planned target dose divided by total number of subjects treated), ORR (proportion of subjects with the best overall response (BOR) of sCR+CR+ VGPR+PR at Months 3 and 6, as determined by local investigator using the IMWG Criteria (Kumar et al., Lancet Oncol. 2016 August; 17(8):e328-e346, herein incorporated by reference in its entirety)), CRR (proportion of subjects with the BOR of sCR+CR at Month 3, as determined by local investigator using the IMWG Criteria), DOR as assessed by local investigator (the time from achievement of sCR+CR+ VGPR+PR to relapse or death due to MM), qPCR-detected transgene of CART concentrations over time in peripheral blood and bone marrow, as well as summary of pre-existing and treatment induced immunogenicity (cellular and humoral) of BCMA CAR-T cell therapy.

**Inclusion Criteria are as Follows:**

subjects with MM who are relapsed and/or refractory to at least 2 prior treatment regimens, including an IMiD (e.g. lenalidomide or pomalidomide), a proteasome inhibitor (e.g. bortezomib, carfilzomib), and an approved anti-CD38 antibody (e.g. daratumumab), if available, and have documented evidence of disease progression (IMWG criteria); measurable disease as defined by the protocol; ECOG performance status that is either 0 or 1 at screening; adequate hematological values; and

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must have a leukapheresis material of nonmobilized cells accepted for manufacturing.

**Exclusion Criteria are as Follows:**

prior administration of a genetically modified cellular product including prior BCMA CAR-T therapy. Patients who have received prior BCMA-directed bispecific antibodies or antibody-drug conjugates (ADC) are not excluded; autologous HSCT within 6 weeks prior to enrollment or any prior history of allogeneic hematopoietic stem cell transplant (HSCT); chemotherapy or any concomitant anti-cancer therapies (other than protocol prescribed lymphodepletion (LD) chemotherapy) within 2 weeks prior to apheresis; treatment with small molecule targeted antineoplastics within 2 weeks of apheresis collection or 5 half-lives whichever is shorter; and have received antibodies or immunotherapies (other than daratumumab) within 4 weeks prior to apheresis collection. Daratumumab within 3 weeks prior to apheresis collection.

**Example 13: Evaluation of BCMA/CD19 Diabody CART**

The efficacy of the CD19 antigen responsive element in the novel single chain diabody CARTs is evaluated using the NALM-6 luciferized model.  $1 \times 10^6$  NALM-6 Luc cells are implanted through lateral tail vein injection on day -7 from CART dosing. Body weight is taken, and in vivo bioluminescent imaging (BLI) is performed to evaluate tumor progression twice a week. Animals are measured twice a week, and once tumor burden reaches  $3 \times 10^6$  photon flux (photons/second), animals are randomized to their particular group (day-1). On day 0, the diabody CAR-Ts are removed from liquid nitrogen and defrosted for injection.  $1 \times 10^6$  double CAR positive cells are injected through the lateral tail vein. Experimental evaluation is conducted over the course of several weeks to determine which construct has the best functional efficacy by evaluating the decrease in BLI over time.

**EQUIVALENTS**

The disclosures of each and every patent, patent application, and publication cited herein are hereby incorporated herein by reference in their entirety. While this invention has been disclosed with reference to certain embodiments, it is apparent that further embodiments and variations of this invention may be devised by others skilled in the art without departing from the true spirit and scope of the invention. The appended claims are intended to be construed to include all such embodiments and equivalent variations.

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SEQUENCE LISTING

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<160> NUMBER OF SEQ ID NOS: 417

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<210> SEQ ID NO 1
<211> LENGTH: 21
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

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-continued

## peptide

&lt;400&gt; SEQUENCE: 1

Met	Ala	Leu	Pro	Val	Thr	Ala	Leu	Leu	Leu	Pro	Leu	Ala	Leu	Leu	Leu
1							5				10				15
His Ala Ala Arg Pro															
20															

&lt;210&gt; SEQ ID NO 2

&lt;211&gt; LENGTH: 45

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 2

Thr	Thr	Thr	Pro	Ala	Pro	Arg	Pro	Pro	Thr	Pro	Ala	Pro	Thr	Ile	Ala
1								5			10			15	
Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly															
20 25 30															
Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp															
35 40 45															

&lt;210&gt; SEQ ID NO 3

&lt;211&gt; LENGTH: 230

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 3

Glu	Ser	Lys	Tyr	Gly	Pro	Pro	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Phe
1									5			10		15	
Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr															
20 25 30															
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val															
35 40 45															
Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val															
50 55 60															
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser															
65 70 75 80															
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu															
85 90 95															
Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser															
100 105 110															
Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro															
115 120 125															
Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln															
130 135 140															
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala															
145 150 155 160															
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr															
165 170 175															
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu															
180 185 190															
Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser															
195 200 205															

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Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser  
 210 215 220

Leu Ser Leu Gly Lys Met  
 225 230

<210> SEQ ID NO 4  
 <211> LENGTH: 282  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 4

Arg Trp Pro Glu Ser Pro Lys Ala Gln Ala Ser Ser Val Pro Thr Ala  
 1 5 10 15

Gln Pro Gln Ala Glu Gly Ser Leu Ala Lys Ala Thr Thr Ala Pro Ala  
 20 25 30

Thr Thr Arg Asn Thr Gly Arg Gly Glu Glu Lys Lys Lys Glu Lys  
 35 40 45

Glu Lys Glu Glu Gln Glu Arg Glu Thr Lys Thr Pro Glu Cys Pro  
 50 55 60

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

Asp Leu Trp Leu Arg Asp Lys Ala Thr Phe Thr Cys Phe Val Val Gly  
 85 90 95

Ser Asp Leu Lys Asp Ala His Leu Thr Trp Glu Val Ala Gly Lys Val  
 100 105 110

Pro Thr Gly Gly Val Glu Glu Gly Leu Leu Glu Arg His Ser Asn Gly  
 115 120 125

Ser Gln Ser Gln His Ser Arg Leu Thr Leu Pro Arg Ser Leu Trp Asn  
 130 135 140

Ala Gly Thr Ser Val Thr Cys Thr Leu Asn His Pro Ser Leu Pro Pro  
 145 150 155 160

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

Leu Ser Leu Asn Leu Leu Ala Ser Ser Asp Pro Pro Glu Ala Ala Ser  
 180 185 190

Trp Leu Leu Cys Glu Val Ser Gly Phe Ser Pro Pro Asn Ile Leu Leu  
 195 200 205

Met Trp Leu Glu Asp Gln Arg Glu Val Asn Thr Ser Gly Phe Ala Pro  
 210 215 220

Ala Arg Pro Pro Gln Pro Gly Ser Thr Thr Phe Trp Ala Trp Ser  
 225 230 235 240

Val Leu Arg Val Pro Ala Pro Pro Ser Pro Gln Pro Ala Thr Tyr Thr  
 245 250 255

Cys Val Val Ser His Glu Asp Ser Arg Thr Leu Leu Asn Ala Ser Arg  
 260 265 270

Ser Leu Glu Val Ser Tyr Val Thr Asp His  
 275 280

<210> SEQ ID NO 5  
 <211> LENGTH: 10  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

-continued

## peptide

&lt;400&gt; SEQUENCE: 5

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

&lt;210&gt; SEQ ID NO 6

&lt;211&gt; LENGTH: 24

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 6

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

Ser	Leu	Val	Ile	Thr	Leu	Tyr	Cys
		20					

&lt;210&gt; SEQ ID NO 7

&lt;211&gt; LENGTH: 42

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 7

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

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

Pro	Glu	Glu	Glu	Gly	Cys	Glu	Leu
	35			40			

&lt;210&gt; SEQ ID NO 8

&lt;211&gt; LENGTH: 48

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 8

Gln	Arg	Arg	Lys	Tyr	Arg	Ser	Asn	Lys	Gly	Glu	Ser	Pro	Val	Glu	Pro
1				5			10		15						

Ala	Glu	Pro	Cys	Arg	Tyr	Ser	Cys	Pro	Arg	Glu	Glu	Gly	Ser	Thr
	20			25			30							

Ile	Pro	Ile	Gln	Glu	Asp	Tyr	Arg	Lys	Pro	Glu	Pro	Ala	Cys	Ser	Pro
	35			40			45								

&lt;210&gt; SEQ ID NO 9

&lt;211&gt; LENGTH: 112

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 9

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

Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr

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20	25	30
Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys		
35	40	45
Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys		
50	55	60
Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg		
65	70	75
Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala		
85	90	95
Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg		
100	105	110

<210> SEQ ID NO 10  
<211> LENGTH: 112  
<212> TYPE: PRT  
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 10

Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly			
1	5	10	15
Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr			
20	25	30	
Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys			
35	40	45	
Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys			
50	55	60	
Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg			
65	70	75	80
Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala			
85	90	95	
Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg			
100	105	110	

<210> SEQ ID NO 11  
<211> LENGTH: 1184  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 11

cgtgaggcgc	cgggtccccgt	cagtggcgag	agcgcacatc	gcccacagtc	cccgagaagt	60
tggggggagg	ggtcggcaat	tgaaccggtg	cctagagaag	gtggcgcggg	gtaaactggg	120
aaagtgtatgt	cgtgtactgg	ctccgcctt	ttcccgagg	tgggggagaa	ccgtatataa	180
gtgcagtagt	cgcgcgtgaac	gttcttttc	gcaacgggtt	tgcgcgcaga	acacaggtaa	240
gtgccgtgt	tggttcccgc	gggcctggcc	tcttacggg	ttatggccct	tgcgtgcctt	300
gaattacttc	cacctggctg	cagtacgtga	ttcttgatcc	cgagcttcgg	tttggaaagt	360
ggtgggagag	ttcgaggcct	tgcgottaag	gagcccccttc	gcctcggtct	tgatgtgagg	420
cctggcctgg	gctgtggggc	cgccgcgtgc	gaatctggtg	gcacccctcgc	gcctgtctcg	480
ctgctttcga	taagtctcta	gccattnaa	attttgatg	acctgtcg	acgcgttttt	540
tctggcaaga	tagtctgt	aatgcgggccc	aagatctgca	cactggatt	tcggtttttg	600
ggcccgccggg	cgccgacggg	gcccgtgcgt	cccagcgcac	atgttcggcg	aggcggggcc	660

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tgcgagcgcg	gcccacggaga	atcgacgggg	ggtagtctca	agctggccgg	cctgtctgg	720
tgcctggcct	cgcgccggcg	tgtatcgccc	cgcctgggg	ggcaaggctg	gccccgtcg	780
caccagttgc	gtgagcgaa	agatggccgc	ttcccggecc	tgctgcaggg	agctcaaaaat	840
ggaggacgctg	gctgcggga	gagggggcg	gtgagtcacc	cacacaagg	aaaagggcct	900
ttccgtctc	agccgtcgct	tcatgtgact	ccacggagta	ccgggcccgg	tccaggcacc	960
tcgattagtt	ctcgagctt	tggagtagt	cgtctttagg	ttggggggag	gggtttatg	1020
cgatggagtt	tccccacact	gagtgggtgg	agactgaagt	taggccagct	tggcacttga	1080
tgtaattctc	cttggaaattt	gcccccttgc	agtttggatc	ttggttcatt	ctcaagcctc	1140
agacagtgg	tcaaagtttt	tttcttccat	ttcaggtgtc	gtga		1184

&lt;210&gt; SEQ ID NO 12

&lt;211&gt; LENGTH: 63

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

&lt;400&gt; SEQUENCE: 12

atggccctgc	ctgtgacagc	cctgtgtctg	cctctggctc	tgctgtgc	tgccgctaga	60
ccc						63

&lt;210&gt; SEQ ID NO 13

&lt;211&gt; LENGTH: 135

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 13

accacgacgc	cagcgccg	accaccaaca	ccggcgccca	ccatcgctc	gcagccctg	60
tccctgccc	cagaggcgtg	ccggccageg	gcggggggcg	cagtgcacac	gagggggctg	120
gacttcgct	gtgat					135

&lt;210&gt; SEQ ID NO 14

&lt;211&gt; LENGTH: 690

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 14

gagagcaagt	acggccctcc	ctgccccct	tgccctgccc	ccgagttcct	ggcgaccc	60
agcgtgttcc	tgttcccccc	caagcccaag	gacaccctga	tgatcagccg	gaccccccag	120
gtgacctgtg	tgggtgggaa	cgtgtcccag	gaggaccccg	aggccatgtt	caactggtag	180
gtggacggcg	tggaggtgca	caacgccaag	accaagcccc	gggaggagca	gttcaatagc	240
acctaaccggg	tgggtgtccgt	gctgaccctg	ctgcaccagg	actggctgaa	cgccaaggaa	300
tacaagtgt	aggtgtccaa	caagggcctg	cccagcagca	tcgagaaaac	catcggcaag	360
gccaaggggcc	agcctcgaaa	gccccaggtg	tacaccctgc	cccctagcca	agaggagatg	420
accaagaacc	aggtgtccct	gacctgcctg	gtgaaggggct	tctaccctag	cgacatcgcc	480
gtggagtgaa	agagcaacgg	ccagcccgag	aacaactaca	agaccacccc	ccctgtgtc	540

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gacagcgacg gcagcttctt cctgtacago cggctgaccg tggacaagag ccggtgccag	600
gaggggcaacg tcttttagctg ctccgtgatg cacgaggecc tgcacaacca ctacaccag	660
aagagcctga gctgtccct gggcaagatg	690

<210> SEQ ID NO 15  
<211> LENGTH: 847  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 15

aggtggcccg aaagtcccaa ggcccaggca tctagtgttc ctactgcaca gccccaggca	60
gaaggcgacc tagccaaagc tactactgca cctgccacta cgcgcaatac tggccgtggc	120
ggggaggaga agaaaaagga gaaagagaaa gaagaacagg aagagaggga gaccaagacc	180
cctgaatgtc catccatac ccagccgctg ggctgtatcc tcttgactcc cgcgtacag	240
gacttgtggc ttagagataa ggccacctt acatgtttcg tctgtggctc tgacctgaag	300
gatgcccatt tgacttggga gggtgcggga aaggtaaccca caggggggggt tgaggaagg	360
ttgctggagc gccattccaa tggctctag agccagcact caagactcac cttccgaga	420
tccctgtgga acgccccggac ctctgtcaca tgtactctaa atcatectag cctgccccca	480
cagcgtctga tggcccttag agagccagcc gcccaggcac cagttaagct tagcctgaat	540
ctgctcgcca gtagtgtatcc cccagagggc gccagctggc tcttatgcga agtgtccggc	600
tttagccgc ccaacatctt gctcatgtgg ctggaggacc agcgagaagt gaacaccagc	660
ggcttcgctc cagccccggcc cccacccctag ccgggttcta ccacattctg ggcctggagt	720
gtcttaaggg tcccagcacc acctagcccc cagccagccca catacacctg tggagggttcc	780
catgaagata gcaggaccct gctaaatgtc tctaggagtc tggagggttcc ctacgtgact	840
gaccatt	847

<210> SEQ ID NO 16  
<211> LENGTH: 30  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 16

ggtggcggag gttctggagg tggagggttcc	30
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<210> SEQ ID NO 17  
<211> LENGTH: 72  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 17

atctacatct gggcgccctt ggccggact tgggggtcc ttctctgtc actggttatc	60
accctttact gc	72

<210> SEQ ID NO 18  
<211> LENGTH: 126  
<212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 18

aaaacggggca gaaagaaaact cctgtatata ttcaaacaac catttatgag accagtacaa	60
actactcaag aggaagatgg ctgtagctgc cgatttccag aagaagaaga aggaggatgt	120
gaacttg	126

<210> SEQ ID NO 19

<211> LENGTH: 123  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 19

aggagtaaga ggagcaggct cctgcacagt gactacatga acatgactcc ccggccccc	60
gggccccaccc gcaagcatta ccagccctat gccccaccac gcgacttcgc agcctatcgc	120
tcc	123

<210> SEQ ID NO 20

<211> LENGTH: 336  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 20

agagtgaagt tcagcaggag cgcagacgcc cccgcgtaca agcagggcca gaaccagctc	60
tataacgagc tcaatctagg acgaagagag gagtacgtatg ttttggacaa gagacgtggc	120
cgggaccctg agatgggggg aaagccgaga aggaagaacc ctcaggaagg cctgtacaat	180
gaactgcaga aagataagat ggcggaggcc tacagtgaga ttggatgaa aggcgagcgc	240
cggagggggca aggggcacga tggccttac caggtctca gtacagccac caaggacacc	300
tacgacgccc ttcacatgca ggccctgccc cctcg	336

<210> SEQ ID NO 21

<211> LENGTH: 336  
<212> TYPE: DNA  
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 21

agagtgaagt tcagcaggag cgcagacgcc cccgcgtacc agcagggcca gaaccagctc	60
tataacgagc tcaatctagg acgaagagag gagtacgtatg ttttggacaa gagacgtggc	120
cgggaccctg agatgggggg aaagccgaga aggaagaacc ctcaggaagg cctgtacaat	180
gaactgcaga aagataagat ggcggaggcc tacagtgaga ttggatgaa aggcgagcgc	240
cggagggggca aggggcacga tggccttac caggtctca gtacagccac caaggacacc	300
tacgacgccc ttcacatgca ggccctgccc cctcg	336

<210> SEQ ID NO 22

<211> LENGTH: 373  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:

-continued

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 22

Pro	Gly	Trp	Phe	Leu	Asp	Ser	Pro	Asp	Arg	Pro	Trp	Asn	Pro	Pro	Thr
1							5			10			15		
Phe	Ser	Pro	Ala	Leu	Leu	Val	Val	Thr	Glu	Gly	Asp	Asn	Ala	Thr	Phe
						20		25					30		
Thr	Cys	Ser	Phe	Ser	Asn	Thr	Ser	Glu	Ser	Phe	Val	Leu	Asn	Trp	Tyr
						35		40				45			
Arg	Met	Ser	Pro	Ser	Asn	Gln	Thr	Asp	Lys	Leu	Ala	Ala	Phe	Pro	Glu
						50		55			60				
Asp	Arg	Ser	Gln	Pro	Gly	Gln	Asp	Cys	Arg	Phe	Arg	Val	Thr	Gln	Leu
						65		70		75		80			
Pro	Asn	Gly	Arg	Asp	Phe	His	Met	Ser	Val	Val	Arg	Ala	Arg	Arg	Asn
						85		90			95				
Asp	Ser	Gly	Thr	Tyr	Leu	Cys	Gly	Ala	Ile	Ser	Leu	Ala	Pro	Lys	Ala
					100		105				110				
Gln	Ile	Lys	Glu	Ser	Leu	Arg	Ala	Glu	Leu	Arg	Val	Thr	Glu	Arg	Arg
					115		120			125					
Ala	Glu	Val	Pro	Thr	Ala	His	Pro	Ser	Pro	Ser	Pro	Arg	Pro	Ala	Gly
					130		135			140					
Gln	Phe	Gln	Thr	Leu	Val	Thr	Thr	Pro	Ala	Pro	Arg	Pro	Pro	Thr	
					145		150			155			160		
Pro	Ala	Pro	Thr	Ile	Ala	Ser	Gln	Pro	Leu	Ser	Leu	Arg	Pro	Glu	Ala
					165		170			175					
Cys	Arg	Pro	Ala	Ala	Gly	Gly	Ala	Val	His	Thr	Arg	Gly	Leu	Asp	Phe
					180		185			190					
Ala	Cys	Asp	Ile	Tyr	Ile	Trp	Ala	Pro	Leu	Ala	Gly	Thr	Cys	Gly	Val
					195		200			205					
Leu	Leu	Leu	Ser	Leu	Val	Ile	Thr	Leu	Tyr	Cys	Lys	Arg	Gly	Arg	Lys
					210		215			220					
Lys	Leu	Leu	Tyr	Ile	Phe	Lys	Gln	Pro	Phe	Met	Arg	Pro	Val	Gln	Thr
					225		230			235			240		
Thr	Gln	Glu	Asp	Gly	Cys	Ser	Cys	Arg	Phe	Pro	Glu	Glu	Glu		
					245		250			255					
Gly	Gly	Cys	Glu	Leu	Arg	Val	Lys	Phe	Ser	Arg	Ser	Ala	Asp	Ala	Pro
					260		265			270					
Ala	Tyr	Lys	Gln	Gly	Gln	Asn	Gln	Leu	Tyr	Asn	Glu	Leu	Asn	Leu	Gly
					275		280			285					
Arg	Arg	Glu	Glu	Tyr	Asp	Val	Leu	Asp	Lys	Arg	Arg	Gly	Arg	Asp	Pro
					290		295			300					
Glu	Met	Gly	Gly	Lys	Pro	Arg	Arg	Lys	Asn	Pro	Gln	Glu	Gly	Leu	Tyr
					305		310			315			320		
Asn	Glu	Leu	Gln	Lys	Asp	Lys	Met	Ala	Glu	Ala	Tyr	Ser	Glu	Ile	Gly
					325		330			335			340		
Met	Lys	Gly	Glu	Arg	Arg	Gly	Lys	Gly	His	Asp	Gly	Leu	Tyr	Gln	
					340		345			350			355		
Gly	Leu	Ser	Thr	Ala	Thr	Lys	Asp	Thr	Tyr	Asp	Ala	Leu	His	Met	Gln
					360		365								
Ala	Leu	Pro	Pro	Arg											
					370										

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100	105	110
Arg Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser		
115	120	125
Leu Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg		
130	135	140
Val Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser		
145	150	155
Pro Arg Pro Ala Gly Gln Phe Gln Thr Leu Val Thr Thr Thr Pro Ala		
165	170	175
Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser		
180	185	190
Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr		
195	200	205
Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala		
210	215	220
Gly Thr Cys Gly Val Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys		
225	230	235
Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met		
245	250	255
Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe		
260	265	270
Pro Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg		
275	280	285
Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn		
290	295	300
Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg		
305	310	315
Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro		
325	330	335
Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala		
340	345	350
Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His		
355	360	365
Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp		
370	375	380
Ala Leu His Met Gln Ala Leu Pro Pro Arg		
385	390	

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<210> SEQ ID NO 25
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 25

Gly Gly Gly Gly Ser
1      5

<210> SEQ ID NO 26
<211> LENGTH: 30
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polypeptide
<220> FEATURE:

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<221> NAME/KEY: MISC\_FEATURE  
 <222> LOCATION: (1)..(30)  
 <223> OTHER INFORMATION: This sequence may encompass 1-6 "Gly Gly Gly Gly Ser" repeating units  
 <220> FEATURE:  
 <223> OTHER INFORMATION: See specification as filed for detailed description of substitutions and preferred embodiments

&lt;400&gt; SEQUENCE: 26

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

Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser  
 20 25 30

<210> SEQ ID NO 27  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 27

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

Gly Gly Gly Ser  
 20

<210> SEQ ID NO 28  
 <211> LENGTH: 15  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 28

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

<210> SEQ ID NO 29  
 <211> LENGTH: 4  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 29

Gly Gly Gly Ser  
 1

<210> SEQ ID NO 30  
 <211> LENGTH: 5000  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide  
 <220> FEATURE:  
 <221> NAME/KEY: misc\_feature  
 <222> LOCATION: (1)..(5000)  
 <223> OTHER INFORMATION: This sequence may encompass 50-5000 nucleotides

&lt;400&gt; SEQUENCE: 30

aaaaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 60

aaaaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 120

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aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa	4920
aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa	4980
aaaaaaaaaaa aaaaaaaaaaa	5000

<210> SEQ ID NO 31  
<211> LENGTH: 100  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 31  
ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt 60  
ttttttttt ttttttttt ttttttttt ttttttttt 100

<210> SEQ ID NO 32  
<211> LENGTH: 5000  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide  
<220> FEATURE:  
<221> NAME/KEY: misc\_feature  
<222> LOCATION: (1)..(5000)  
<223> OTHER INFORMATION: This sequence may encompass 50-5000 nucleotides

<400> SEQUENCE: 32  
ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt 60  
ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt 120  
ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt 180  
ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt 240  
ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt 300  
ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt 360  
ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt 420  
ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt 480  
ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt 540  
ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt 600  
ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt 660  
ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt 720  
ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt 780  
ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt 840  
ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt 900  
ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt 960  
ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt 1020  
ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt 1080  
ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt 1140  
ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt 1200  
ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt 1260

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ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt	3720
ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt	3780
ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt	3840
ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt	3900
ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt	3960
ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt	4020
ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt	4080
ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt	4140
ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt	4200
ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt	4260
ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt	4320
ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt	4380
ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt	4440
ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt	4500
ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt	4560
ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt	4620
ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt	4680
ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt	4740
ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt	4800
ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt	4860
ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt	4920
ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt	4980
ttttttttt ttttttttt	5000

<210> SEQ ID NO 33  
 <211> LENGTH: 5000  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 polynucleotide  
 <220> FEATURE:  
 <221> NAME/KEY: misc\_feature  
 <222> LOCATION: (1)..(5000)  
 <223> OTHER INFORMATION: This sequence may encompass 100-5000  
 nucleotides

<400> SEQUENCE: 33

aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa	60
aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa	120
aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa	180
aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa	240
aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa	300
aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa	360
aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa	420
aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa	480

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<210> SEQ ID NO 34
<211> LENGTH: 400
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(400)
<223> OTHER INFORMATION: This sequence may encompass 100-400 nucleotides

<400> SEQUENCE: 34

aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa 60
aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa 120
aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa 180
aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa 240
aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa 300
aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa 360
aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa 400

<210> SEQ ID NO 35
<211> LENGTH: 2000
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(2000)
<223> OTHER INFORMATION: This sequence may encompass 50-2000 nucleotides

<400> SEQUENCE: 35

aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa 60
aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa 120
aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa 180
aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa 240
aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa 300
aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa 360
aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa 420
aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa 480
aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa 540
aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa 600
aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa 660
aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa 720
aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa 780
aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa 840
aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa 900
aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa 960
aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa 1020
aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa 1080
aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa 1140
aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa 1200
aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa aaaaaaaaaaa 1260

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aaaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	1320
aaaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	1380
aaaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	1440
aaaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	1500
aaaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	1560
aaaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	1620
aaaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	1680
aaaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	1740
aaaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	1800
aaaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	1860
aaaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	1920
aaaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	1980
aaaaaaaaaaa	aaaaaaaaaa						2000

&lt;210&gt; SEQ ID NO 36

&lt;211&gt; LENGTH: 41

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 36

Arg	Ser	Lys	Arg	Ser	Arg	Leu	Leu	His	Ser	Asp	Tyr	Met	Asn	Met	Thr
1						5		10				15			

Pro	Arg	Arg	Pro	Gly	Pro	Thr	Arg	Lys	His	Tyr	Gln	Pro	Tyr	Ala	Pro
						20		25				30			

Pro	Arg	Asp	Phe	Ala	Ala	Tyr	Arg	Ser
		35				40		

&lt;210&gt; SEQ ID NO 37

&lt;211&gt; LENGTH: 123

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 37

aggagtaaga	ggagcaggct	cctgcacagt	gactacatga	acatgactcc	ccggcgcccc	60
ggggccaccc	gcaaggattta	ccagccctat	gccccaccac	gcatgttcgc	agcctatcgc	120
tcc						123

&lt;210&gt; SEQ ID NO 38

&lt;211&gt; LENGTH: 35

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 38

Thr	Lys	Lys	Tyr	Ser	Ser	Ser	Val	His	Asp	Pro	Asn	Gly	Glu	Tyr
1							5				10		15	

Met Phe Met Arg Ala Val Asn Thr Ala Lys Lys Ser Arg Leu Thr Asp

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20

25

30

Val Thr Leu  
35

<210> SEQ ID NO 39  
<211> LENGTH: 105  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 39

acaaaaaaaaaga agtattcatc cagtgtgcac gaccctaacg gtgaatacat gttcatgaga	60
gcagtgaaca cagccaaaaa atccagactc acagatgtga cccta	105

<210> SEQ ID NO 40  
<211> LENGTH: 30  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

&lt;400&gt; SEQUENCE: 40

ggtggcgagg gttctggagg tgggggttcc	30
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<210> SEQ ID NO 41  
<211> LENGTH: 4  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 41

Gly Gly Gly Ser  
1

<210> SEQ ID NO 42  
<211> LENGTH: 40  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide  
<220> FEATURE:  
<221> NAME/KEY: MISC\_FEATURE  
<222> LOCATION: (1)..(40)  
<223> OTHER INFORMATION: This sequence may encompass 1-10 "Gly Gly Gly Ser" repeating units

&lt;400&gt; SEQUENCE: 42

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

Gly Gly Gly Ser Gly Gly Ser Gly Gly Gly Ser Gly Gly Ser			
20	25		30
	30		

Gly Gly Gly Ser Gly Gly Ser	
35	40

<210> SEQ ID NO 43  
<211> LENGTH: 18  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

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## peptide

&lt;400&gt; SEQUENCE: 43

Gly	Ser	Thr	Ser	Gly	Ser	Gly	Lys	Pro	Gly	Ser	Gly	Glu	Gly	Ser	Thr
1				5			10					15			

Lys Gly

&lt;210&gt; SEQ ID NO 44

&lt;211&gt; LENGTH: 5

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 44

Ser	Tyr	Ala	Met	Ser
1				5

&lt;210&gt; SEQ ID NO 45

&lt;211&gt; LENGTH: 17

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 45

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

Gly

&lt;210&gt; SEQ ID NO 46

&lt;211&gt; LENGTH: 14

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 46

Arg	Glu	Trp	Val	Pro	Tyr	Asp	Val	Ser	Trp	Tyr	Phe	Asp	Tyr
1				5			10						

&lt;210&gt; SEQ ID NO 47

&lt;211&gt; LENGTH: 7

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 47

Gly	Phe	Thr	Phe	Ser	Ser	Tyr
1				5		

&lt;210&gt; SEQ ID NO 48

&lt;211&gt; LENGTH: 6

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 48

Ser Gly Ser Gly Gly Ser

-continued

1 5

<210> SEQ ID NO 49  
<211> LENGTH: 8  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 49

Gly Phe Thr Phe Ser Ser Tyr Ala  
1 5

<210> SEQ ID NO 50  
<211> LENGTH: 8  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 50

Ile Ser Gly Ser Gly Gly Ser Thr  
1 5

<210> SEQ ID NO 51  
<211> LENGTH: 16  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 51

Ala Arg Arg Glu Trp Val Pro Tyr Asp Val Ser Trp Tyr Phe Asp Tyr  
1 5 10 15

<210> SEQ ID NO 52  
<211> LENGTH: 123  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 52

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

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

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

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

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

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

Ala Arg Arg Glu Trp Val Pro Tyr Asp Val Ser Trp Tyr Phe Asp Tyr  
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser  
115 120

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<210> SEQ ID NO 53  
<211> LENGTH: 369  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 53

gaagtgcagt	tgctggagtc	aggcggagga	ctgggtgcgc	ccggaggatc	gcttcgcctg	60
agctgcgcag	cctcaggctt	tactttctcc	tcctacgcca	tgtcctgggt	cagacaggtt	120
cccgaaaaagg	gactggaaatg	ggtgtccgc	attagcggtt	ccggcgaaag	cacttactat	180
ccccactctg	tgaagggccg	cttcaactatc	tcccgggaca	actccaagaa	caccctgtat	240
ctccaaatga	atccctgag	ggccgaagat	accgcggtgt	actactgcgc	tagacgggag	300
tgggtgcct	acgatgtcag	ctggtaacttc	gactactggg	gacagggcac	tctcgtgact	360
gtgtccctcc						369

<210> SEQ ID NO 54  
<211> LENGTH: 11  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 54

Arg	Ala	Ser	Gln	Ser	Ile	Ser	Ser	Tyr	Leu	Asn
1					5				10	

<210> SEQ ID NO 55  
<211> LENGTH: 7  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 55

Ala	Ala	Ser	Ser	Lue	Gln	Ser
1				5		

<210> SEQ ID NO 56  
<211> LENGTH: 9  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 56

Gln	Gln	Ser	Tyr	Ser	Thr	Pro	Lue	Thr
1					5			

<210> SEQ ID NO 57  
<211> LENGTH: 7  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 57

Ser Gln Ser Ile Ser Ser Tyr

-continued

1 5

<210> SEQ ID NO 58  
<211> LENGTH: 3  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 58

Ala Ala Ser  
1

<210> SEQ ID NO 59  
<211> LENGTH: 6  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 59

Ser Tyr Ser Thr Pro Leu  
1 5

<210> SEQ ID NO 60  
<211> LENGTH: 6  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 60

Gln Ser Ile Ser Ser Tyr  
1 5

<210> SEQ ID NO 61  
<211> LENGTH: 107  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 61

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly  
1 5 10 15Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr  
20 25 30Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile  
35 40 45Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly  
50 55 60Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro  
65 70 75 80Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Leu  
85 90 95Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys  
100 105<210> SEQ ID NO 62  
<211> LENGTH: 321

-continued

<212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 62

```

gacattcaaa tgactcagtc cccgtccctcc ctctccgcct ccgtgggaga tcgcgtcacg      60
atcacgtgca gggccagcca gagcatctcc agtacatcgta actggatccca gcagaaggcca    120
gggaaggcac cgaagtcctt gatctacgcc gctagtcgc tgcagtccgg cgcccttca     180
cggttctcgat cggccggctc aggaccggac ttccaccctga ccattagcag cctgcaggcg    240
gaggacttcg cgacatacta ctgtcagcag tcatactcca cccctctgac cttcggccaa     300
gggaccaaag tggagatcaa g                                         321

```

<210> SEQ ID NO 63  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 63

```

Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly
1           5           10          15
Gly Gly Gly Ser
20

```

<210> SEQ ID NO 64  
 <211> LENGTH: 250  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 64

```

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1           5           10          15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20          25          30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35          40          45
Ser Ala Ile Ser Gly Ser Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50          55          60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65          70          75          80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85          90          95
Ala Arg Arg Glu Trp Val Pro Tyr Asp Val Ser Trp Tyr Phe Asp Tyr
100         105         110
Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser
115         120         125
Gly Gly Gly Ser Gly Gly Ser Gly Gly Gly Ser Asp
130         135         140
Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
145         150         155         160
Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu

```

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-continued

165	170	175
-----	-----	-----

Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr 180	185	190
--	-----	-----

Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser 195	200	205
--	-----	-----

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu 210	215	220
--	-----	-----

Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Leu Thr 225	230	235	240
--	-----	-----	-----

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys 245	250
--	-----

&lt;210&gt; SEQ ID NO 65

&lt;211&gt; LENGTH: 750

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 65

gaaagtgcagt	tgcgtggagtc	aggcggagga	ctgggtgcagc	ccggaggatc	gcttcgcctt	60
agctgcgcag	cctcaggctt	taccttctcc	tcctacgcca	tgtcctgggt	cagacaggct	120
cccgggaagg	gactgaaatg	ggtgtccgcc	attagcggtt	ccggcggaag	cacttactat	180
ggcgactctg	tgaaggggccg	cttcaactatc	tcccgggaca	actccaagaa	caccctgtat	240
ctcccaaatga	atcccctgag	ggccgaagat	accgcggtgt	actactgcgc	tagacgggag	300
tgggtgcctt	acgatgtcag	ctggtaacttc	gactactggg	gacagggcac	tctcgtgact	360
gtgtccctccg	gtgggttgtgg	atcgggggggt	ggtggttcgg	gcggaggagg	atctggagga	420
ggaggggtcgg	acattcaaat	gactcagtcc	ccgtcctccc	tctccgcctc	cgtggagat	480
cgcgtcacga	tcacgtcag	ggccagccag	agcatctcca	gctacctgaa	ctggtaccag	540
cagaagccag	ggaaggcacc	gaagtcctg	atctacgccc	ctagctcgct	gcagtccgc	600
gtcccttcac	ggttctcggg	atcgggctca	ggcaccgact	tcaccctgac	cattagcagc	660
ctgcagccgg	aggacttcgc	gacatactac	tgtcagcagt	catactccac	ccctctgacc	720
ttcggccaag	ggaccaaagt	ggagatcaag				750

&lt;210&gt; SEQ ID NO 66

&lt;211&gt; LENGTH: 473

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 66

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

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

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

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

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

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-continued

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
   85               90               95  
 Ala Arg Arg Glu Trp Val Pro Tyr Asp Val Ser Trp Tyr Phe Asp Tyr  
   100              105              110  
 Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser  
   115              120              125  
 Gly Gly Gly Ser Gly Gly Ser Gly Gly Gly Ser Asp  
   130              135              140  
 Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp  
   145              150              155              160  
 Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu  
   165              170              175  
 Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
   180              185              190  
 Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
   195              200              205  
 Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu  
   210              215              220  
 Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Leu Thr  
   225              230              235              240  
 Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Thr Thr Thr Pro Ala Pro  
   245              250              255  
 Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu  
   260              265              270  
 Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg  
   275              280              285  
 Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly  
   290              295              300  
 Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys  
   305              310              315              320  
 Arg Gly Arg Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg  
   325              330              335  
 Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro  
   340              345              350  
 Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser  
   355              360              365  
 Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu  
   370              375              380  
 Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg  
   385              390              395              400  
 Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln  
   405              410              415  
 Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr  
   420              425              430  
 Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Gly Lys Gly His Asp  
   435              440              445  
 Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala  
   450              455              460  
 Leu His Met Gln Ala Leu Pro Pro Arg  
   465              470

<210> SEQ ID NO 67  
 <211> LENGTH: 1419

-continued

<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 67

```

gaagtgcagt tgctggagtc aggccggaggca ctgggtgcagc ccggaggatc gcttcgcttg      60
agctgcgcag cctcaggcatt taccttctcc tcctacgcca tgcgtccgggt cagacaggct      120
cccgaaaagg gactggaatg ggtgtccgccc attagcggtt ccggccggaaag cacttactat      180
ggcgactctg tgaaggggccg cttcaactatc tccccggaca actccaagaa caccctgtat      240
ctcccaaataa attcctctgag ggccgaagat accgcgggtt actactgcgc tagacgggag      300
tgggtgcctt acgtatgtcag ctggtaacttc gactactggg gacaggggcac tctcgtaact      360
gtgtccctcg gttgggtggat atcgggggggt ggtgggttcgg gcggaggagg atctggagga      420
ggagggttcgg acattcaaat gactcagtcg ccgtccctcc tctccgcctc cgtgggagat      480
cgcggtcagca tcacgtgcag ggccaggccag agcatctcca gctacatgaa ctggtaaccag      540
cagaaggccag ggaaggccacc gaagtcctcg atctacgccc ctagctcgct gcagtccggc      600
gtcccttcac ggttctcggt atcgggctca ggcacccgact tcaccctgac cattagcagc      660
ctgcagccgg aggacttcgc gacatactac tgtcagcagt catactccac ccctctgacc      720
ttcggccaaag ggaccaaaatg ggagatcaag accactatccc cagcaccggag gccacccacc      780
ccggctctta ccatcgccctc ccagccctcg tccctgcgtc cggaggcatg tagacccgca      840
gtcggtgggg ccgtgcatac ccgggggtttt gacttcgcct gcgatatactt cattgggcc      900
cctctggctg gtacttgcgg ggttctgtcg ctttactcg tgatcactct ttactgtaa      960
cgcggtcggaa agaagctgt gtacatcttt aagcaaccct tcacatggcc tgcagact      1020
actcaagagg aggacggctg ttcatgcggg ttcccaagagg aggagggaaagg cggctgcgaa      1080
ctgcgcgtga aattcagccg cagcgcagat gctccagccctt accagcaggg gcagaaccag      1140
ctctacaacg aactcaatct tggtcggaga gaggagtcg acgtgtcgaa caagccggaga      1200
ggacccggacc cagaaaatggg ccggaaaggccg cgcggaaaga atccccaaaga gggcctgtac      1260
aaccgagctcc aaaaggataa gatggcagaa gcctatagcg agattggat gaaaggggaa      1320
cgcagaagag gcaaaggccca cgacggactg taccaggac tcagcaccgc caccaaggac      1380
acatatgacg ctcttcacat gcaggccctg ccgcctcg      1419

```

<210> SEQ ID NO 68  
<211> LENGTH: 12  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 68

Arg	Glu	Trp	Trp	Tyr	Asp	Asp	Trp	Tyr	Lys	Asp	Tyr
1					5				10		

<210> SEQ ID NO 69  
<211> LENGTH: 14  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

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-continued

&lt;400&gt; SEQUENCE: 69

```

Ala Arg Arg Glu Trp Trp Tyr Asp Asp Trp Tyr Leu Asp Tyr
1           5           10

```

```

<210> SEQ ID NO 70
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

```

&lt;400&gt; SEQUENCE: 70

```

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

```

```

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

```

```

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

```

```

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

```

```

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

```

```

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

```

```

Ala Arg Arg Glu Trp Trp Tyr Asp Asp Trp Tyr Leu Asp Tyr Trp Gly
100         105         110

```

```

Gln Gly Thr Leu Val Thr Val Ser Ser
115         120

```

```

<210> SEQ ID NO 71
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide

```

&lt;400&gt; SEQUENCE: 71

```

gaagtgcagt tgctggagtc aggeggagga ctgggtgcagc ccggaggatc gcttcgcttg      60
agctgcgcag cctcaggctt tactttctcc tcctacgcca tgtcctgggt cagacaggct      120
cccgaaaaagg gactggaatg ggtgtccgcc attagcggtt ccggcgaaag cacttactat      180
gccgactctg tgaagggccg cttcaactatc tcccggaca actccaagaa caccctgtat      240
ctccaaatga attccctgag ggccgaagat accgcggtgtt actactgcgc tagacggag      300
tggtggtacg acgattggta cctggactac tggggacagg gcactctcgt gactgtgtcc      360
tcc

```

```

<210> SEQ ID NO 72
<211> LENGTH: 248
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

```

&lt;400&gt; SEQUENCE: 72

```

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

```

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421

422

-continued

---

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

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

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

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

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

Ala Arg Arg Glu Trp Trp Tyr Asp Asp Trp Tyr Leu Asp Tyr Trp Gly  
100 105 110

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

Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Asp Ile Gln  
130 135 140

Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val  
145 150 155 160

Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn Trp  
165 170 175

Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala  
180 185 190

Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
195 200 205

Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe  
210 215 220

Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Leu Thr Phe Gly  
225 230 235 240

Gln Gly Thr Lys Val Glu Ile Lys  
245

<210> SEQ ID NO 73  
<211> LENGTH: 744  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 73

gaagtgcagt	tgctggagtc	aggcggagga	ctgggtgcagc	ccggaggatc	gcttcgttgc	60
agctgcgcag	cctcaggctt	tactttctcc	tcctacgcca	tgtcctgggt	cagacaggct	120
cccgaaaaagg	gactggaatg	ggtgtccgccc	attagcggtt	ccggcgaaag	cacttactat	180
gccgactctg	tgaaggcccg	cttcactatac	tcccgaaaca	actccaagaa	caccctgttat	240
ctcccaaatga	atccccctgag	ggccgaagat	accgcgggtgt	actactgcgc	tagacgggag	300
tggtggtacg	acgattggta	cctggactac	tggggacagg	gcactctcggt	gactgtgtcc	360
tccgggtgggt	gtggatcggg	gggtgggtgtt	tcggggcggag	gaggatctgg	aggaggaggg	420
tcggacattc	aatgactca	gtccccgtcc	tccctctccg	cctccgtggg	agatcgcgtc	480
acgatcacgt	gcagggccag	ccagagcatc	tccagctacc	tgaactggta	ccagcagaag	540
ccagggaaagg	caccgaagct	cctgatctac	gcccgttagct	cgctgcagtc	cgccgtccct	600
tcacggttct	cgggatcggg	ctcaggcacc	gacttcaccc	tgaccattag	cagcgtcag	660
ccggaggact	tcgcgacata	ctactgtcag	cagtcatact	ccacccctct	gaccttcggc	720

-continued

caaggggacca aagtggagat caag

744

<210> SEQ ID NO 74  
<211> LENGTH: 471  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 74

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

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

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

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

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

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

Ala	Arg	Arg	Glu	Trp	Trp	Tyr	Asp	Asp	Trp	Tyr	Leu	Asp	Tyr	Trp	Gly
							100	105	110						

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

Gly	Gly	Ser	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Ser	Asp	Ile	Gln
							130	135	140				

Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly	Asp	Arg	Val
							145	150	155						

Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Ser	Ile	Ser	Ser	Tyr	Leu	Asn	Trp
							165	170	175						

Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile	Tyr	Ala	Ala
							180	185	190						

Ser	Ser	Leu	Gln	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly	Ser	
							195	200	205					

Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro	Glu	Asp	Phe
							210	215	220						

Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Ser	Tyr	Ser	Thr	Pro	Leu	Thr	Phe	Gly
							225	230	235						

Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys	Thr	Thr	Pro	Ala	Pro	Arg	Pro
							245	250	255					

Pro	Thr	Pro	Ala	Pro	Thr	Ile	Ala	Ser	Gln	Pro	Leu	Ser	Leu	Arg	Pro
							260	265	270						

Glu	Ala	Cys	Arg	Pro	Ala	Ala	Gly	Gly	Ala	Val	His	Thr	Arg	Gly	Leu
							275	280	285						

Asp	Phe	Ala	Cys	Asp	Ile	Tyr	Ile	Trp	Ala	Pro	Leu	Ala	Gly	Thr	Cys
							290	295	300						

Gly	Val	Leu	Leu	Leu	Ser	Leu	Val	Ile	Thr	Leu	Tyr	Cys	Lys	Arg	Gly
							305	310	315						

Arg	Lys	Lys	Leu	Leu	Tyr	Ile	Phe	Lys	Gln	Pro	Phe	Met	Arg	Pro	Val
							325	330	335						

Gln	Thr	Thr	Gln	Glu	Glu	Asp	Gly	Cys	Ser	Cys	Arg	Phe	Pro	Glu	Glu
							340	345	350						

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Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp  
 355                   360                   365

Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn  
 370                   375                   380

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg  
 385                   390                   395                   400

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly  
 405                   410                   415

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu  
 420                   425                   430

Ile Gly Met Lys Gly Glu Arg Arg Gly Lys Gly His Asp Gly Leu  
 435                   440                   445

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His  
 450                   455                   460

Met Gln Ala Leu Pro Pro Arg  
 465                   470

&lt;210&gt; SEQ ID NO 75

&lt;211&gt; LENGTH: 1413

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 75

gaagtgca	tgctggagtc	aggcggagga	ctgggtgc	ccggaggatc	gcttcgc	tg	60
agctgc	cgc	aggc	tttac	tc	tgc	tttgc	120
cccg	ggaa	agg	actggaa	tg	gtcc	gggt	
ccgc	actct	tg	tttact	tc	tc	tttgc	180
gttgc	atcc	tttgc	tttact	tc	tc	tttgc	240
tttgc	atcc	tttgc	tttact	tc	tc	tttgc	300
tttgc	atcc	tttgc	tttact	tc	tc	tttgc	360
tttgc	atcc	tttgc	tttact	tc	tc	tttgc	420
tttgc	atcc	tttgc	tttact	tc	tc	tttgc	480
tttgc	atcc	tttgc	tttact	tc	tc	tttgc	540
tttgc	atcc	tttgc	tttact	tc	tc	tttgc	600
tttgc	atcc	tttgc	tttact	tc	tc	tttgc	660
tttgc	atcc	tttgc	tttact	tc	tc	tttgc	720
tttgc	atcc	tttgc	tttact	tc	tc	tttgc	780
tttgc	atcc	tttgc	tttact	tc	tc	tttgc	840
tttgc	atcc	tttgc	tttact	tc	tc	tttgc	900
tttgc	atcc	tttgc	tttact	tc	tc	tttgc	960
tttgc	atcc	tttgc	tttact	tc	tc	tttgc	1020
tttgc	atcc	tttgc	tttact	tc	tc	tttgc	1080
tttgc	atcc	tttgc	tttact	tc	tc	tttgc	1140
tttgc	atcc	tttgc	tttact	tc	tc	tttgc	1200
tttgc	atcc	tttgc	tttact	tc	tc	tttgc	1260
tttgc	atcc	tttgc	tttact	tc	tc	tttgc	1320

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```
agaggccaaag gccacgacgg actgtaccag ggactcagca cgcgcaccaa ggacacctat    1380
gacgctttc acatgcaggc cctgcgcctt cggtt                                1413
```

```
<210> SEQ ID NO 76
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide
```

&lt;400&gt; SEQUENCE: 76

```
Arg Glu Trp Trp Gly Glu Ser Trp Leu Phe Asp Tyr
1           5          10
```

```
<210> SEQ ID NO 77
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide
```

&lt;400&gt; SEQUENCE: 77

```
Ala Arg Arg Glu Trp Trp Gly Glu Ser Trp Leu Phe Asp Tyr
1           5          10
```

```
<210> SEQ ID NO 78
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polypeptide
```

&lt;400&gt; SEQUENCE: 78

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

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

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

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

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

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

```
Ala Arg Arg Glu Trp Trp Gly Glu Ser Trp Leu Phe Asp Tyr Trp Gly
100         105         110
```

```
Gln Gly Thr Leu Val Thr Val Ser Ser
115         120
```

```
<210> SEQ ID NO 79
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polynucleotide
```

&lt;400&gt; SEQUENCE: 79

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gaagtgca	gtgctggagtc	aggcggagga	ctgggtgc	ccggaggatc	gcttcgctt	60
agctgc	cgtcaggc	tacccctc	tcctacgcca	tgtcctgg	cagacaggct	120
ccccggaa	agg gactgg	aatg ggtgtcc	ccattagcg	tt ccggaa	g cacttactat	180
ggccactc	tgc tgaagg	ggcc	tcc tca	tata cccgg	gaca aagaa	240
ctccaaat	gtgaa	atccctg	gag ggcc	accgcgg	tgt actactgc	300
tggtgggg	aaagctgg	ctgactac	tggggacagg	gcacttcgt	gactgtgtcc	360
tcc						363

<210> SEQ ID NO 80  
<211> LENGTH: 248  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 80

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

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

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

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

Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr
									65						70

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

Ala	Arg	Arg	Glu	Trp	Trp	Gly	Glu	Ser	Trp	Leu	Phe	Asp	Tyr	Trp	Gly
									100						105

Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	Ser	Gly	Gly	
									115						120

Gly	Gly	Ser	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Ser	Asp	Ile	Gln		
									130						135

Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly	Asp	Arg	Val
									145						150

Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Ser	Ile	Ser	Ser	Tyr	Leu	Asn	Trp
									165						170

Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile	Tyr	Ala	Ala
									180						185

Ser	Ser	Leu	Gln	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly	Ser		
									195						200

Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro	Glu	Asp	Phe
									210						215

Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Ser	Tyr	Ser	Thr	Pro	Leu	Thr	Phe	Gly
									225						230

Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys	
								245

<210> SEQ ID NO 81  
<211> LENGTH: 744  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:

-continued

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 81

aaagtgcagt	tgctggagtc	aggcgaggaga	ctgggtgcagc	ccggaggaggatc	gcttcgtttg	60
agctgcgcag	cctcaggcgtt	taccttctcc	tcctacgcca	tgtcctgggt	cagacaggct	120
ccccggaaagg	gactggaatg	ggtgtccgccc	attagcggtt	ccggcggaag	cacttactat	180
ggcgactctg	tgaagggccg	cttcaactatc	tcccgggaca	actccaagaa	caccctgtat	240
ctccaaatga	attccctgag	ggcgcgaagat	accgcgggtt	actactgcgc	tagacgggag	300
tggtgtggag	aaagctggct	gttcgactac	tggggacagg	gcactctcg	gactgtgtcc	360
tcccggtgtt	gtggatcggg	gggtgggtgt	tcggggcggag	gaggatctgg	aggaggagggg	420
tccggacattc	aatgactca	gtccccgtcc	tccctctccg	cctccgtggg	agatcgcgtc	480
acgatcacgt	gcagggccag	ccagagcatc	tccagctacc	tgaactggta	ccagcagaag	540
ccagggaaagg	caccgaagct	cctgatctac	gcccgttagct	cgctgcagtc	cggcgtccct	600
tcacgggtct	cgggatcggg	ctcaggcacc	qacttccacc	tgaccattag	cagctgcag	660
ccggaggact	tcgcgacata	ctactgtcag	cagtcatact	ccacccctct	gaccttcggc	720
caaaqqqacc	aaqtqqaqat	caaq				744

<210> SEQ ID NO 82

<211> LENGTH: 471

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<213> ORGANISM  
<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 82

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

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

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

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

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

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

Ala Arg Arg Glu Trp Trp Gly Glu Ser Trp Leu Phe Asp Tyr Trp Gly  
 100 105 110

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

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln  
 130 135 140

Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val  
145 150 155 160

Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn Trp  
165 170 175

Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala

Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser

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195	200	205
Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe		
210	215	220
Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Leu Thr Phe Gly		
225	230	235
Gln Gly Thr Lys Val Glu Ile Lys Thr Thr Pro Ala Pro Arg Pro		
245	250	255
Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro		
260	265	270
Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu		
275	280	285
Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys		
290	295	300
Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly		
305	310	315
Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val		
325	330	335
Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu		
340	345	350
Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp		
355	360	365
Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn		
370	375	380
Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg		
385	390	395
Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly		
405	410	415
Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu		
420	425	430
Ile Gly Met Lys Gly Glu Arg Arg Gly Lys Gly His Asp Gly Leu		
435	440	445
Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His		
450	455	460
Met Gln Ala Leu Pro Pro Arg		
465	470	

<210> SEQ ID NO 83  
<211> LENGTH: 1413  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 83

gaagtgcagt tgctggagtc aggccggagga ctgggtgcagc ccggaggatc gttcgcttg	60
agctgcgcag cctcaggctt tacttctcc tcctacgcca tgcctcggtt cagacaggct	120
cccgaaaaagg gactggaatg ggtgtccgcc attagcggtt ccggcgaaag cacttactat	180
gccgactctg tgaaggggccg cttcaactatc tcccgggaca actccaagaa caccctgtat	240
ctccaaatga attccctgag ggccgaagat accgcggtgtt actactgcgc tagacggag	300
tggtgggggag aaagctggct gttcgactac tggggacagg gcactctcggt gactgtgtcc	360
tccgggtggtg gtggatcgaaa gggtggtggt tcggggcgag gaggatctgg aggaggagg	420
tcggacattc aatgactca gtccccgtcc tccctctccg cctccgtggg agatcgctc	480

-continued

acgatcacgt gcagggccag ccagagcatc tccagctacc tgaactggta ccagcagaag	540
ccagggaaagg caccgaagct cctgatctac gccgctagct cgctgcagtc cggcgccct	600
tcacggttct cgggatcggg ctcaggcacc gacttcaccc tgaccattag cagcctgcag	660
ccggaggact tcgcgcacata ctactgtcag cagtctactt ccacccctct gacccctggc	720
caagggacca aagtggagat caagaccact accccagcac cgaggccacc caccggct	780
cctaccatcg cctcccaagcc tctgtccctg cggtccggagg catgttagacc cgctgcgtt	840
ggggccgtgc atacccgggg tcttgacttgc gcttgcgata tctacatttggccccctctg	900
gctggtaactt gccccggctt gctgtttca ctcgtgtatc ctctttacttgc taagcgcgg	960
cggaagaagc tgctgtacat cttaagcaa cccttcatga ggccctgtgca gactactcaa	1020
gaggaggacg gctgttcatg ccgggtccca gaggaggagg aaggcggctg cgaactgcgc	1080
gtgaaattca gcccgcgc agatgctcca gcctaccaggc aggggcagaa ccagctctac	1140
aacgaactca atcttggtcg gagagaggag tacgacgtgc tggacaagcgg gagaggacgg	1200
gacccagaaa tgggcgggaa gccgcgcaga aagaatcccc aagaggccct gtacaacgag	1260
ctccaaaagg ataagatggc agaaggcttat agcgagattt gatatgaaagg ggaacgcaga	1320
agaggcggaaag gccacgacgg actgttaccag ggactcagca ccggccaccaa ggacacctat	1380
gacgcttc acatgcaggc cctgcgcctt cgg	1413

<210> SEQ\_ID NO 84  
<211> LENGTH: 14  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide  
<220> FEATURE:  
<221> NAME/KEY: MOD\_RES  
<222> LOCATION: (4)..(4)  
<223> OTHER INFORMATION: V or absent  
<220> FEATURE:  
<221> NAME/KEY: MOD\_RES  
<222> LOCATION: (5)..(5)  
<223> OTHER INFORMATION: P or absent  
<220> FEATURE:  
<221> NAME/KEY: MOD\_RES  
<222> LOCATION: (6)..(6)  
<223> OTHER INFORMATION: W or Y  
<220> FEATURE:  
<221> NAME/KEY: MOD\_RES  
<222> LOCATION: (7)..(7)  
<223> OTHER INFORMATION: G, Y, or D  
<220> FEATURE:  
<221> NAME/KEY: MOD\_RES  
<222> LOCATION: (8)..(8)  
<223> OTHER INFORMATION: E, D, or V  
<220> FEATURE:  
<221> NAME/KEY: MOD\_RES  
<222> LOCATION: (9)..(9)  
<223> OTHER INFORMATION: S or D  
<220> FEATURE:  
<221> NAME/KEY: MOD\_RES  
<222> LOCATION: (11)..(11)  
<223> OTHER INFORMATION: L or Y  
<220> FEATURE:  
<221> NAME/KEY: MOD\_RES  
<222> LOCATION: (12)..(12)  
<223> OTHER INFORMATION: F or L

&lt;400&gt; SEQUENCE: 84

Arg Glu Trp Xaa Xaa Xaa Xaa Xaa Trp Xaa Xaa Asp Tyr

-continued

```

<210> SEQ ID NO 85
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      peptide
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: V or absent
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: P or absent
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: W or Y
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: G, Y, or D
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (10)..(10)
<223> OTHER INFORMATION: E, D, or V
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (11)..(11)
<223> OTHER INFORMATION: S or D
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (13) ..(13)
<223> OTHER INFORMATION: L or Y
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (14)..(14)
<223> OTHER INFORMATION: F or L

<400> SEQUENCE: 85

```

Ala Arg Arg Glu Trp Xaa Xaa Xaa Xaa Xaa Trp Xaa Xaa Asp Tyr  
 1               5               10               15

```

<210> SEQ ID NO 86
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      peptide

<400> SEQUENCE: 86

```

Ser Tyr Gly Met His  
 1               5

```

<210> SEQ ID NO 87
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      peptide

<400> SEQUENCE: 87

```

Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys  
 1               5               10               15

Gly

```

<210> SEQ ID NO 88
<211> LENGTH: 14

```

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<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 88

Ser Gly Tyr Ala Leu His Asp Asp Tyr Tyr Gly Leu Asp Val  
1 5 10

<210> SEQ ID NO 89  
<211> LENGTH: 6  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 89

Ser Tyr Asp Gly Ser Asn  
1 5

<210> SEQ ID NO 90  
<211> LENGTH: 8  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 90

Gly Phe Thr Phe Ser Ser Tyr Gly  
1 5

<210> SEQ ID NO 91  
<211> LENGTH: 8  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 91

Ile Ser Tyr Asp Gly Ser Asn Lys  
1 5

<210> SEQ ID NO 92  
<211> LENGTH: 16  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 92

Gly Gly Ser Gly Tyr Ala Leu His Asp Asp Tyr Tyr Gly Leu Asp Val  
1 5 10 15

<210> SEQ ID NO 93  
<211> LENGTH: 123  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 93

Gln Val Gln Leu Gln Glu Ser Gly Gly Val Val Gln Pro Gly Arg

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1	5	10	15												
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Ser	Tyr
				20					25				30		
Gly	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
	35				40				45						
Ala	Val	Ile	Ser	Tyr	Asp	Gly	Ser	Asn	Lys	Tyr	Tyr	Ala	Asp	Ser	Val
	50				55			60							
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr
	65				70			75		80					
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
	85					90		95							
Gly	Gly	Ser	Gly	Tyr	Ala	Leu	His	Asp	Asp	Tyr	Tyr	Gly	Leu	Asp	Val
	100					105			110						
Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser					
					115			120							

&lt;210&gt; SEQ ID NO 94

&lt;211&gt; LENGTH: 369

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 94

caagtgcagc tgcaggaatc cggtgccgga gtcgtgcagc ctggaggag cctgagactc	60
tcatgcgcgc cgtcagggtt cacctttcc tcctacggga tgcattgggt cagacaggcc	120
cccgaaagg gactcgaatg ggtggctgtg atcagctacg acggctccaa caagtactac	180
gccgactccg tgaaaggccg gttcaactatc tccccggaca actccaagaa cacgctgtat	240
ctgcaaatga attcaactgcg cgccgaggat accgctgtgt actactgcgg tggctccggt	300
tacgcccgc acgatgacta ttacggcctt gacgtctggg gccaggaaac cctcgtaact	360
gtgtccagc	369

&lt;210&gt; SEQ ID NO 95

&lt;211&gt; LENGTH: 14

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 95

Thr	Gly	Thr	Ser	Ser	Asp	Val	Gly	Gly	Tyr	Asn	Tyr	Val	Ser	
1					5			10						

&lt;210&gt; SEQ ID NO 96

&lt;211&gt; LENGTH: 7

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 96

Asp	Val	Ser	Asn	Arg	Pro	Ser
1				5		

&lt;210&gt; SEQ ID NO 97

&lt;211&gt; LENGTH: 11

-continued

<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 97

Ser Ser Tyr Thr Ser Ser Thr Leu Tyr Val  
1 5 10

<210> SEQ ID NO 98  
<211> LENGTH: 10  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 98

Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr  
1 5 10

<210> SEQ ID NO 99  
<211> LENGTH: 3  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 99

Asp Val Ser  
1

<210> SEQ ID NO 100  
<211> LENGTH: 8  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 100

Tyr Thr Ser Ser Ser Thr Leu Tyr  
1 5

<210> SEQ ID NO 101  
<211> LENGTH: 9  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 101

Ser Ser Asp Val Gly Gly Tyr Asn Tyr  
1 5

<210> SEQ ID NO 102  
<211> LENGTH: 111  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 102

Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln

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-continued

1	5	10	15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr			
20	25	30	
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu			
35	40	45	
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe			
50	55	60	
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu			
65	70	75	80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser			
85	90	95	
Ser Thr Leu Tyr Val Phe Gly Ser Gly Thr Lys Val Thr Val Leu			
100	105	110	

<210> SEQ ID NO 103  
<211> LENGTH: 333  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 103

cagagcgcac tgactcagcc ggcatccgtg tccggtagcc cggacagtc gattaccatc	60
tcctgtaccc gcacctcctc cgacgtggga gggtacaact acgtgtcggt gtaccaggag	120
caccaggaa agggccctaa gttgtatgtc tacgtatgtt caaacggcc gtctggagtc	180
tccaacgggt tctccggctc caagtccggc aacaccgcca gcctgaccat tagcgggctg	240
caagccgagg atgaggccga ctactactgc tcgagctaca catcctcgag caccctctac	300
gtgttcggct cggggactaa ggtcacccgtg ctg	333

<210> SEQ ID NO 104  
<211> LENGTH: 15  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 104

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

<210> SEQ ID NO 105  
<211> LENGTH: 249  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 105

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

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

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

Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val		
50	55	60

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-continued

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

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

Gly Gly Ser Gly Tyr Ala Leu His Asp Asp Tyr Tyr Gly Leu Asp Val  
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser  
115 120 125

Gly Gly Gly Ser Gly Gly Ser Gln Ser Ala Leu Thr Gln  
130 135 140

Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys  
145 150 155 160

Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr  
165 170 175

Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Asp Val Ser  
180 185 190

Asn Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly  
195 200 205

Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala  
210 215 220

Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser Ser Thr Leu Tyr Val Phe  
225 230 235 240

Gly Ser Gly Thr Lys Val Thr Val Leu  
245

<210> SEQ ID NO 106  
<211> LENGTH: 747  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 106

```

caagtgcagc tgcaggaaatc cggggccgga gtcgtgcagc ctggaaaggag cctgagactc      60
tcatgcgcgc cgtcagggtt cacttttcc tccatacgga tgcattgggt cagacaggcc      120
ccccggaaagg gactcaaatg ggtggctgtg atcagctacg acggctccaa caagtactac      180
gccgactccg tgaaaggccg gttcaactatc tcccggaca actccaagaa cacgctgtat      240
ctgc当地atga attcaactgcg cgcggaggat accgctgtgt actactgcgg tggctccggt      300
tacgcccctgc acgatgacta ttacggcctt gacgtctggg gccagggAAC cctcgtgact      360
gtgtccagcg gtggaggagg ttccggccgga ggaggatca gagggggtgg atcgcagagc      420
gcactgactc agccggcatc cgtgtccggt agccccggac agtcgattac catctcctgt      480
accggcacct cctccgacgt gggagggtac aactacgtgt cgtggatcca gcagcaccca      540
ggaaaggccc ctaagtttat gatctacgtat gtgtcaaacc gcccgtctgg agtctccaa      600
cggttctccg gctccaagtc cggcaacacc gccagcctga ccattagccg gctgcaagcc      660
gaggatgagg ccgactacta ctgctcgago tacacatcct cgagcacccct ctacgtttc      720
ggctcgggaa ctaaggtcac cgtgctg                                747

```

<210> SEQ ID NO 107  
<211> LENGTH: 472  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence

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-continued

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 107

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

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

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

Ala	Val	Ile	Ser	Tyr	Asp	Gly	Ser	Asn	Lys	Tyr	Tyr	Ala	Asp	Ser	Val
							50	55		60					

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

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

Gly	Gly	Ser	Gly	Tyr	Ala	Leu	His	Asp	Asp	Tyr	Tyr	Gly	Leu	Asp	Val
							100	105		110					

Trp	Gly	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	Ser		
							115	120		125					

Gly	Gly	Gly	Ser	Gly	Gly	Gly	Ser	Gly	Ser	Ala	Leu	Thr	Gln		
							130	135		140					

Pro	Ala	Ser	Val	Ser	Gly	Ser	Pro	Gly	Gln	Ser	Ile	Thr	Ile	Ser	Cys
							145	150		155		160			

Thr	Gly	Thr	Ser	Ser	Asp	Val	Gly	Gly	Tyr	Asn	Tyr	Val	Ser	Trp	Tyr
							165	170		175					

Gln	Gln	His	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Met	Ile	Tyr	Asp	Val	Ser
							180	185		190					

Asn	Arg	Pro	Ser	Gly	Val	Ser	Asn	Arg	Phe	Ser	Gly	Ser	Lys	Ser	Gly
							195	200		205					

Asn	Thr	Ala	Ser	Leu	Thr	Ile	Ser	Gly	Leu	Gln	Ala	Glu	Asp	Glu	Ala
							210	215		220					

Asp	Tyr	Tyr	Cys	Ser	Ser	Tyr	Thr	Ser	Ser	Thr	Leu	Tyr	Val	Phe	
							225	230		235		240			

Gly	Ser	Gly	Thr	Lys	Val	Thr	Val	Leu	Thr	Thr	Thr	Pro	Ala	Pro	Arg
							245	250		255					

Pro	Pro	Thr	Pro	Ala	Pro	Thr	Ile	Ala	Ser	Gln	Pro	Leu	Ser	Leu	Arg
							260	265		270					

Pro	Glu	Ala	Cys	Arg	Pro	Ala	Ala	Gly	Gly	Ala	Val	His	Thr	Arg	Gly
							275	280		285					

Leu	Asp	Phe	Ala	Cys	Asp	Ile	Tyr	Ile	Trp	Ala	Pro	Leu	Ala	Gly	Thr
							290	295		300					

Cys	Gly	Val	Leu	Leu	Leu	Ser	Leu	Val	Ile	Thr	Leu	Tyr	Cys	Lys	Arg
							305	310		315		320			

Gly	Arg	Lys	Lys	Leu	Leu	Tyr	Ile	Phe	Lys	Gln	Pro	Phe	Met	Arg	Pro
							325	330		335					

Val	Gln	Thr	Thr	Gln	Glu	Glu	Asp	Gly	Cys	Ser	Cys	Arg	Phe	Pro	Glu
							340	345		350					

Glu	Glu	Gly	Gly	Cys	Glu	Leu	Arg	Val	Lys	Phe	Ser	Arg	Ser	Ala	
							355	360		365					

Asp	Ala	Pro	Ala	Tyr	Gln	Gln	Gly	Gly	Gln	Asn	Gln	Leu	Tyr	Asn	Glu	Leu
							370	375		380						

Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly

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-continued

385	390	395	400
Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu			
405	410	415	
Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser			
420	425	430	
Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly			
435	440	445	
Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu			
450	455	460	
His Met Gln Ala Leu Pro Pro Arg			
465	470		

<210> SEQ ID NO 108  
<211> LENGTH: 1416  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 108

caagtgcagc tgcaggaaatc cggtggcgga gtcgtgcagc ctggaaggag cctgagactc	60
tcatgcgccc cgtcagggtt cacctttcc tcctacggga tgcattgggt cagacaggcc	120
ccccggaaagg gactcgaatg ggtggctgtg atcagctacg acggctccaa caagtactac	180
ggcgactccg tgaaaggccg gttcaactatc tccgggaca actccaagaa cacgctgtat	240
ctgcaaatga attcaactgcg cgcggaggat accgctgtgt actactgcgg tggctccggt	300
tacgcccctgc acgatgacta ttacggcctt gacgtctggg gccagggAAC cctcgtgact	360
gtgtccagcg gtggaggagg ttccggcgga ggaggatca gagggggtgg atcgcagagc	420
gcactgactc agccggcatc cgtgtccggt agccccggac agtcgattac catctctgt	480
accggcacct cctccgacgt gggagggtac aactacgtgt cgtggatcca gcagcaccca	540
ggaaaggccc ctaagttgat gatctacgt gtgtcaaacc gcccgtctgg agtctccaac	600
cggttctccg gtcctaagtc cggcaacacc gccagcctga ccattagcgg gctcaagcc	660
gaggatgagg ccgactacta ctgctcgago tacacatcc ctacgtttc	720
ggctcgggga ctaaggtcac cgtgtcgacc actaccccaag caccggggcc accccacccg	780
gctcctacca tcgcctccca gcctctgtcc ctgcgtccgg aggcatgtag acccgcagct	840
ggtgtggccg tgcatacccg gggcttgac ttgcctcgcg atatctacat ttggggccct	900
ctggctggta cttgcggggt cctgtgtctt tcactcgta tcactttta ctgtaagcgc	960
ggtcggaaga agctgtgtca cattttaag caacccttca tgaggtctgt gcagactact	1020
caagaggagg acggctgttc atgcgggttc ccagaggagg aggaaggccg ctgcgaactg	1080
cgcgtgaaat tcaagccgcag cgcagatgtc ccagcctacc agcaggggca gaaccagctc	1140
tacaacgaac tcaatcttgg tcggagagag gagtacgacg tgctggacaa gcggagagga	1200
cgggaccacag aaatggccgg gaagccgcgc agaaagaatc cccaagaggg cctgtacaac	1260
gagctccaaa aggataagat ggcagaagcc tatagcgaga ttggtatgaa aggggaacgc	1320
agaagaggca aaggccacga cggactgtac cagggactca gcaccgcccac caaggacacc	1380
tatgacgctc ttcacatgca ggccctgcgg cctcggt	1416

<210> SEQ ID NO 109  
<211> LENGTH: 17

-continued

<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 109

Val	Ile	Ser	Tyr	Lys	Gly	Ser	Asn	Lys	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5				10						15	

Gly

<210> SEQ ID NO 110  
<211> LENGTH: 6  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 110

Ser	Tyr	Lys	Gly	Ser	Asn
1				5	

<210> SEQ ID NO 111  
<211> LENGTH: 8  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 111

Ile	Ser	Tyr	Lys	Gly	Ser	Asn	Lys
1				5			

<210> SEQ ID NO 112  
<211> LENGTH: 123  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 112

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

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

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

Ala	Val	Ile	Ser	Tyr	Lys	Gly	Ser	Asn	Lys	Tyr	Tyr	Ala	Asp	Ser	Val
				50				55			60				

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

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

Gly	Gly	Ser	Gly	Tyr	Ala	Leu	His	Asp	Asp	Tyr	Tyr	Gly	Leu	Asp	Val
				100				105			110				

Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser
				115				120		

<210> SEQ ID NO 113  
<211> LENGTH: 369

-continued

<212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 113

```
caagtgcagc ttgtcgaatc gggaggcgga gtgggtgcagc ctggacgatc gctccggctc      60
tcatgtgcgc cgagcggatt cacttctcg agctacggc tgcactgggt cagacaagcc      120
ccagggaaagg gcctggaatg ggtggctgtc atctcgatca agggctcaaa caagtactac      180
ggcgactccg tgaagggccg gttcaccatc tccccgcata actccaagaa taccctctat      240
ctgcaaatga acagcctgag ggccgaggat actgcagtgt actactgcgg gggttcaggc      300
tacgcgtgc acgacgacta ctacggattt gacgtctggg gccaaggaac tcttgtgacc      360
gtgtccctct                                369
```

<210> SEQ ID NO 114  
 <211> LENGTH: 7  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 114

```
Glu Val Ser Asn Arg Leu Arg
1           5
```

<210> SEQ ID NO 115  
 <211> LENGTH: 11  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 115

```
Ser Ser Tyr Thr Ser Ser Ser Ala Leu Tyr Val
1           5           10
```

<210> SEQ ID NO 116  
 <211> LENGTH: 3  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 116

```
Glu Val Ser
1
```

<210> SEQ ID NO 117  
 <211> LENGTH: 8  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 117

```
Tyr Thr Ser Ser Ser Ala Leu Tyr
1           5
```

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-continued

<210> SEQ ID NO 118  
<211> LENGTH: 111  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 118

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

Ser	Ile	Thr	Ile	Ser	Cys	Thr	Gly	Thr	Ser	Ser	Asp	Val	Gly	Gly	Tyr
	20				25							30			

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

Met	Ile	Tyr	Glu	Val	Ser	Asn	Arg	Leu	Arg	Gly	Val	Ser	Asn	Arg	Phe
	50				55					60					

Ser	Gly	Ser	Lys	Ser	Gly	Asn	Thr	Ala	Ser	Leu	Thr	Ile	Ser	Gly	Leu
65				70					75			80			

Gln	Ala	Glu	Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Ser	Ser	Tyr	Thr	Ser	Ser
	85			90					95						

Ser	Ala	Leu	Tyr	Val	Phe	Gly	Ser	Gly	Thr	Lys	Val	Thr	Val	Leu
	100				105					110				

<210> SEQ ID NO 119  
<211> LENGTH: 333  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 119

cagagcgcgc	tgactcagcc	tgcctccgtg	agcggttcgc	cgggacagtc	cattaccatt	60
tcgtgcacccg	ggacacctc	tcgcacgtggga	ggctacaact	acgtgtccctg	gtaccagcag	120
catccccggaa	aggccccgaa	gctgtatgatc	tacgaagtgt	cgaacagact	gcggggagtc	180
tccaaccgc	tttccgggtc	caagtccggc	aacaccgc	gcctgaccat	cagcgggctc	240
caggcagaag	atgaggctga	ctattactgc	tcctcctaca	cgtcaagctc	cgcctctac	300
gtgttcgggt	ccgggaccaa	agtcaactgt	ctg			333

<210> SEQ ID NO 120  
<211> LENGTH: 254  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 120

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

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

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

Ala	Val	Ile	Ser	Tyr	Lys	Gly	Ser	Asn	Lys	Tyr	Tyr	Ala	Asp	Ser	Val
	50				55				60						

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

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-continued

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
                   85                  90                  95  
  
 Gly Gly Ser Gly Tyr Ala Leu His Asp Asp Tyr Tyr Gly Leu Asp Val  
                   100                105                110  
  
 Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser  
                   115                120                125  
  
 Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln  
                   130                135                140  
  
 Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser  
                   145                150                155                160  
  
 Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn  
                   165                170                175  
  
 Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met  
                   180                185                190  
  
 Ile Tyr Glu Val Ser Asn Arg Leu Arg Gly Val Ser Asn Arg Phe Ser  
                   195                200                205  
  
 Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln  
                   210                215                220  
  
 Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser Ser  
                   225                230                235                240  
  
 Ala Leu Tyr Val Phe Gly Ser Gly Thr Lys Val Thr Val Leu  
                   245                250

```
<210> SEQ ID NO 121
<211> LENGTH: 762
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide
```

<400> SEQUENCE: 121  
caagtgcagc ttgtcgaatc gggaggcgga gtggtgacg ctggacgatc gctccggctc 60  
tcatgtgccg cgagcggatt caccttcgtc agctacggca tgcactgggt cagacaagcc 120  
ccagggaaagg gccttggaaatg ggtggctgtc atctcgatc agggctcaaa caagtactac 180  
ggcgactccg tgaaggccg gttcaccatc tccccgcata actccaaagaa taccccttat 240  
ctgcaaatga acagcctgag ggccgaggat actgcagtgt actactcggtt gggttcaggc 300  
tacgcgcgtc acgacgacta ctacggattt gacgtctggg gcacaaaggaaac tctttgtacc 360  
gtgtccctctg gtggaggcggt atcagggggtt ggccggatctg ggggttgttgg ttccggggga 420  
ggaggatcgc agagcgcgtc gactcagctt gcctccgtga gcgggttcggcc gggacagttcc 480  
attaccattt cgtgcaccgg gaccccttcc gacgtggggag gctacaacta cgtgtccctgg 540  
taccagcagc atcccgaaa gggcccgaaag ctgtatgtatc acgaagtgtc gaacagactg 600  
cggggagttt ccaaccgtt ttccgggtcc aagtccggca acaccggccag cctgaccatc 660  
agcggggatcc aggcagaaga tgaggctgac tattactgtct cctccatcac gtcaagctcc 720  
qccctctacq tqtttcqqqtc cqqqqaccaaaa qtcactqtqtc tq 762

<210> SEQ ID NO 122  
<211> LENGTH: 477  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
polypeptide

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-continued

&lt;400&gt; SEQUENCE: 122

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

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

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

Ala Val Ile Ser Tyr Lys Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val  
 50               55               60

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

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

Gly Gly Ser Gly Tyr Ala Leu His Asp Asp Tyr Tyr Gly Leu Asp Val  
 100              105              110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser  
 115              120              125

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

Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser  
 145              150              155              160

Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn  
 165              170              175

Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met  
 180              185              190

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

Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln  
 210              215              220

Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser Ser  
 225              230              235              240

Ala Leu Tyr Val Phe Gly Ser Gly Thr Lys Val Thr Val Leu Thr Thr  
 245              250              255

Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln  
 260              265              270

Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala  
 275              280              285

Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala  
 290              295              300

Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Ser Leu Val Ile Thr  
 305              310              315              320

Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln  
 325              330              335

Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser  
 340              345              350

Cys Arg Phe Pro Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys  
 355              360              365

Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln  
 370              375              380

Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu  
 385              390              395              400

Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg

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-continued

405	410	415
Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met		
420	425	430
Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly		
435	440	445
Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp		
450	455	460
Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg		
465	470	475

<210> SEQ ID NO 123  
<211> LENGTH: 1431  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 123

```

caagtgcagc ttgtcgaatc gggaggcgga gtgggcagc ctggacgatc gctccggctc      60
tcatgtgcgc cgagcggatt cacttctcg agtacggca tgcactgggt cagacaagcc      120
ccagggaaagg gccttggatg ggtggctgtc atctcgatac agggctaaa caagtactac      180
ggcgactccg tgaaggcccg gttcaccatc tccccgcata actccaagaa taccctctat      240
ctgcaaatga acagcctgag ggccgaggat actgcagtgt actactgcgg gggttcaggc      300
tacgcgtgc acgacgacta ctacggattt gacgtctggg gccaaggaac tcttgtgacc      360
gtgtcccttg gtggaggcggt atcagggggat ggeggatctg ggggtgggtt ttccggggga      420
ggaggatcgc agagcgcgcgt gactcagccgc tcctccgtga ggggttcggcc gggacagtcc      480
attaccattt cgtgcaccgg gaccccttcc gacgtggag gctacaacta cgtgcctgg      540
taccagcagc atcccgaaa ggccccgaag ctgtatgtt acgaagtgtc gaacagactg      600
cggggagtc ccaacccgtt ttccgggtcc aagtccggca acaccgcacg cctgaccatc      660
agcgggtcc accgagaaga tgaggctgac tattactgtc cctcctacac gtcaagctcc      720
gccctctacg tgttcgggtc cgggacccaa gtcactgtgc tgaccactac cccagcacccg      780
aggccaccca ccccggtcc taccatcgc tccccgcgtc tgccctgcg tccggaggca      840
tgttagacccg cagctgggtt ggccgtgcgtt acccggttgc ttgacttcgc ctgcgtatcc      900
tacattttggg cccctctggc ttgtacttgc ggggtctgc tgctttact cgtgtact      960
ctttactgtt agcgcgggtcg gaagaagctg ctgtacatct ttaagcaacc cttcatgagg      1020
cctgtgcaga ctactcaaga ggaggacggc ttgcattgc ggttcccaga ggaggaggaa      1080
ggcggctcg aactgcgcgt gaaattcago cgcagcgcag atgcgtccacg ctaccagcag      1140
gggcagaacc agctctacaa cgaactcaat cttggcggaa gagaggagta cgacgtgtc      1200
gacaagcggc gaggacggga cccagaaatg ggcgggaaacg cgcgcagaaa gaatccccaa      1260
gagggcctgt acaacgagct cccaaaggat aagatggcag aagcctatag cgagatttgt      1320
atgaaagggg aacgcagaag aggcaaggg cacgacggc tgcattccagg actcagcacc      1380
gccaccaagg acaccttatga cgctttcac atgcaggccc tgccgcctcg g      1431

```

<210> SEQ ID NO 124  
<211> LENGTH: 111  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:

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**465****466**

-continued

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 124

Gln	Ser	Ala	Leu	Thr	Gln	Pro	Ala	Ser	Val	Ser	Gly	Ser	Pro	Gly	Gln
1					5				10					15	
Ser	Ile	Thr	Ile	Ser	Cys	Thr	Gly	Thr	Ser	Ser	Asp	Val	Gly	Gly	Tyr
	20					25							30		
Asn	Tyr	Val	Ser	Trp	Tyr	Gln	Gln	His	Pro	Gly	Lys	Ala	Pro	Lys	Leu
	35					40					45				
Met	Ile	Tyr	Glu	Val	Ser	Asn	Arg	Leu	Arg	Gly	Val	Ser	Asn	Arg	Phe
	50					55				60					
Ser	Gly	Ser	Lys	Ser	Gly	Asn	Thr	Ala	Ser	Leu	Thr	Ile	Ser	Gly	Leu
	65				70				75			80			
Gln	Ala	Glu	Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Ser	Ser	Tyr	Thr	Ser	Ser
	85					90						95			
Ser	Thr	Leu	Tyr	Val	Phe	Gly	Ser	Gly	Thr	Lys	Val	Thr	Val	Leu	
	100					105						110			

&lt;210&gt; SEQ ID NO 125

&lt;211&gt; LENGTH: 333

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 125

cagagcgcgc	tgactcagcc	tgcctccgtg	agegggttcgc	cgggacagtc	cattaccatt	60
tcgtgcaccg	ggacctccctc	cgacgtggga	ggctacaact	acgtgtccctg	gtaccagcag	120
catcccgaa	aggccccgaa	gctgatgato	tacgaagtgt	cgaacagact	gcggggagtc	180
tccaaccgct	tttccgggtc	caagtccggc	aacaccgcca	gcctgaccat	cagcgggctc	240
caggcagaag	atgaggctga	cttattactgc	tcctccctaca	cgtcaagctc	caccctctac	300
gtgttcgggt	ccgggaccaa	agtcaactgtg	ctg			333

&lt;210&gt; SEQ ID NO 126

&lt;211&gt; LENGTH: 254

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 126

Gln	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Val	Val	Gln	Pro	Gly	Arg	
1					5				10				15		
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Ser	Tyr
	20					25					30				
Gly	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
	35				40					45					
Ala	Val	Ile	Ser	Tyr	Lys	Gly	Ser	Asn	Lys	Tyr	Tyr	Ala	Asp	Ser	Val
	50					55			60						
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr
	65					70			75			80			
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
	85					90						95			
Gly	Gly	Ser	Gly	Tyr	Ala	Leu	His	Asp	Asp	Tyr	Tyr	Gly	Leu	Asp	Val

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-continued

100	105	110	
Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser			
115	120	125	
Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln			
130	135	140	
Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser			
145	150	155	160
Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn			
165	170	175	
Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met			
180	185	190	
Ile Tyr Glu Val Ser Asn Arg Leu Arg Gly Val Ser Asn Arg Phe Ser			
195	200	205	
Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln			
210	215	220	
Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser Ser			
225	230	235	240
Thr Leu Tyr Val Phe Gly Ser Gly Thr Lys Val Thr Val Leu			
245	250		

<210> SEQ ID NO 127  
<211> LENGTH: 762  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 127

caagtgcagc ttgtcaatc gggaggcgga gtgggtgcagc ctggacgatc gctccggctc	60
tcatgtgccg cgagcggatt caccttctcg agctacggca tgcactgggt cagacaagcc	120
ccaggaaagg gcctggaatg ggtggctgtc atctcgata agggctaaa caagtactac	180
gccgactccg tgaagggccg gttaccatc tcccgcgata actccaagaa tacccttat	240
ctgcaaatga acagcctgag ggccgaggat actgcagtgt actactgcgg gggttcaggc	300
tacgcgtgc acgacgacta ctacggattt gacgtctggg gccaaaggAAC tcttgtgacc	360
gtgtcctctg gtggaggcgg atcaggggggt ggccggatctg ggggtgggtgg ttccggggga	420
ggaggatcgc agagcgcgct gactcagcct gcctccgtga gcggttcgcc gggacagtcc	480
attaccattt cgtgcaccgg gacctcttc gacgtggag gctacaacta cgtgtcctgg	540
taccagcagc atccccggaaa ggccccgaag ctgatgatct acgaagtgtc gaacagactg	600
cggggagtct ccaaccgctt ttccgggtcc aagtccggca acaccgcccAG cctgaccatc	660
agcgggctcc aggccagaaga tgaggctgac tattactgct cctcctacac gtcaagctcc	720
accctctacg ttttcgggtc cgggacaaa gtcactgtgc tg	762

<210> SEQ ID NO 128  
<211> LENGTH: 477  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 128

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

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-continued

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr  
 20 25 30  
 Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45  
 Ala Val Ile Ser Tyr Lys Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val  
 50 55 60  
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr  
 65 70 75 80  
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95  
 Gly Gly Ser Gly Tyr Ala Leu His Asp Asp Tyr Tyr Gly Leu Asp Val  
 100 105 110  
 Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser  
 115 120 125  
 Gly Gly Gly Ser Gly Gly Ser Gly Gly Gly Ser Gln  
 130 135 140  
 Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser  
 145 150 155 160  
 Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn  
 165 170 175  
 Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met  
 180 185 190  
 Ile Tyr Glu Val Ser Asn Arg Leu Arg Gly Val Ser Asn Arg Phe Ser  
 195 200 205  
 Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln  
 210 215 220  
 Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser Ser  
 225 230 235 240  
 Thr Leu Tyr Val Phe Gly Ser Gly Thr Lys Val Thr Val Leu Thr Thr  
 245 250 255  
 Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln  
 260 265 270  
 Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala  
 275 280 285  
 Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala  
 290 295 300  
 Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Ser Leu Val Ile Thr  
 305 310 315 320  
 Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln  
 325 330 335  
 Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser  
 340 345 350  
 Cys Arg Phe Pro Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys  
 355 360 365  
 Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln  
 370 375 380  
 Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu  
 385 390 395 400  
 Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg  
 405 410 415  
 Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met  
 420 425 430

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471

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-continued

Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly  
435 440 445

Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp  
450 455 460

Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg  
465 470 475

&lt;210&gt; SEQ ID NO 129

&lt;211&gt; LENGTH: 1431

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 129

caagtgcagc ttgtcgaatc gggaggcgga gtgggtgcagc ctggacgatc gctccggctc 60  
 tcatgtgcgg cgagcggatt caccttctcg agctacggca tgcactgggt cagacaagcc 120  
 ccaggaaagg gcctggaatg ggtggctgtc atctcgatca aaggctcaaa caagtactac 180  
 gcccactccg tgaagggccg gttcaccatc tcccgcgata actccaagaa taccctctat 240  
 ctgcaaatga acagcctgag ggccgaggat actgcagtgt actactgcgg ggttcaggc 300  
 tacgcgctgc acgacgacta ctacggattt gacgtctggg gccaaggAAC tcttgtgacc 360  
 gtgtcctctg gtggaggcggt atcagggggtt ggcggatctg ggggtgggtgg ttccggggga 420  
 ggaggatcgc agagcgcgct gactcagctt gctccgtga gcggttcggc gggacagtcc 480  
 attaccatTT cgtgcaccgg gacctcctcc gacgtgggag gctacaacta cgtgtcctgg 540  
 taccagcagc atcccgaaa ggccccgaag ctgatgtatc acgaagtgtc gaacagactg 600  
 cggggagtctt ccaaccgcTT ttccgggtcc aagtccggca acaccgcag cctgaccatc 660  
 agcgggctcc aggccagaaga tgaggctgac tattactgtt cctcctacac gtcaagctcc 720  
 accctctacg tgttcgggtc cgccgacaaa gtcactgtgc tgaccactac cccagcacgg 780  
 agggcaccca ccccggtcc taccatgcgc tcccagcctc tgccctgcg tccggaggca 840  
 ttagaccccg cagctgggtgg ggcgtgcattt accgggggtt tgacttcgc ctgcgatatc 900  
 tacatttggg cccctctggc tggtacttgc ggggtcctgc tgctttact cgtgatact 960  
 ctttactgtt agcgcggcgcg gaagaagctt ctgtacatct ttaagcaacc cttcatgagg 1020  
 cctgtgcaga ctactcaaga ggaggacggc tgttcatgcc ggttcccaga ggaggaggaa 1080  
 ggccgcgtgcg aactgcgcgt gaaattcago cgcagcgcag atgcgtccagc ctaccagcag 1140  
 gggcagaacc agctctacaa cgaactcaat cttgggtcgga gagaggagta cgacgtgctg 1200  
 gacaagcggg gaggacgggaa cccagaaatg ggccggaaagc cgccgcagaaa gaatccccaa 1260  
 gagggcctgt acaacgagct ccaaaaggat aagatggcag aagcctatag cgagatttgt 1320  
 atgaaagggg aacgcagaag aggcaaggc cacgacggc tgtaaccaggg actcagcacc 1380  
 gccaccaagg acacctatga cgctttcac atgcaggccc tgccgcctcg g 1431

&lt;210&gt; SEQ ID NO 130

&lt;211&gt; LENGTH: 17

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;220&gt; FEATURE:

&lt;221&gt; NAME/KEY: MOD\_RES

&lt;222&gt; LOCATION: (5) . . . (5)

-continued

&lt;223&gt; OTHER INFORMATION: D or K

&lt;400&gt; SEQUENCE: 130

1	Val Ile Ser Tyr Xaa Gly Ser Asn Lys	Tyr Tyr Ala Asp Ser Val Lys	
	5	10	15

Gly

&lt;210&gt; SEQ ID NO 131

&lt;211&gt; LENGTH: 7

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;220&gt; FEATURE:

&lt;221&gt; NAME/KEY: MOD\_RES

&lt;222&gt; LOCATION: (1)..(1)

&lt;223&gt; OTHER INFORMATION: D or E

&lt;220&gt; FEATURE:

&lt;221&gt; NAME/KEY: MOD\_RES

&lt;222&gt; LOCATION: (6)..(6)

&lt;223&gt; OTHER INFORMATION: P or L

&lt;220&gt; FEATURE:

&lt;221&gt; NAME/KEY: MOD\_RES

&lt;222&gt; LOCATION: (7)..(7)

&lt;223&gt; OTHER INFORMATION: S or R

&lt;400&gt; SEQUENCE: 131

Xaa Val Ser Asn Arg Xaa Xaa

1	5	
---	---	--

&lt;210&gt; SEQ ID NO 132

&lt;211&gt; LENGTH: 11

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;220&gt; FEATURE:

&lt;221&gt; NAME/KEY: MOD\_RES

&lt;222&gt; LOCATION: (8)..(8)

&lt;223&gt; OTHER INFORMATION: T or A

&lt;400&gt; SEQUENCE: 132

Ser Ser Tyr Thr Ser Ser Ser Xaa Leu Tyr Val

1	5	10
---	---	----

&lt;210&gt; SEQ ID NO 133

&lt;211&gt; LENGTH: 6

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;220&gt; FEATURE:

&lt;221&gt; NAME/KEY: MOD\_RES

&lt;222&gt; LOCATION: (3)..(3)

&lt;223&gt; OTHER INFORMATION: D or K

&lt;400&gt; SEQUENCE: 133

Ser Tyr Xaa Gly Ser Asn

1	5	
---	---	--

&lt;210&gt; SEQ ID NO 134

&lt;211&gt; LENGTH: 3

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

-continued

<220> FEATURE:  
<221> NAME/KEY: MOD\_RES  
<222> LOCATION: (1)..(1)  
<223> OTHER INFORMATION: D or E  
  
<400> SEQUENCE: 134

Xaa Val Ser  
1

<210> SEQ ID NO 135  
<211> LENGTH: 8  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide  
<220> FEATURE:  
<221> NAME/KEY: MOD\_RES  
<222> LOCATION: (6)..(6)  
<223> OTHER INFORMATION: T or A

<400> SEQUENCE: 135

Tyr Thr Ser Ser Ser Xaa Leu Tyr  
1 5

<210> SEQ ID NO 136  
<211> LENGTH: 8  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide  
<220> FEATURE:  
<221> NAME/KEY: MOD\_RES  
<222> LOCATION: (4)..(4)  
<223> OTHER INFORMATION: D or K

<400> SEQUENCE: 136

Ile Ser Tyr Xaa Gly Ser Asn Lys  
1 5

<210> SEQ ID NO 137  
<211> LENGTH: 5  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 137

Gly Phe Trp Met Ser  
1 5

<210> SEQ ID NO 138  
<211> LENGTH: 17  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 138

Asn Ile Lys Gln Asp Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val Arg  
1 5 10 15

Gly

<210> SEQ ID NO 139  
<211> LENGTH: 9

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<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 139

Ala Leu Asp Tyr Tyr Gly Met Asp Val  
1 5

<210> SEQ ID NO 140  
<211> LENGTH: 7  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 140

Gly Phe Thr Phe Ser Gly Phe  
1 5

<210> SEQ ID NO 141  
<211> LENGTH: 6  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 141

Lys Gln Asp Gly Ser Glu  
1 5

<210> SEQ ID NO 142  
<211> LENGTH: 8  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 142

Gly Phe Thr Phe Ser Gly Phe Trp  
1 5

<210> SEQ ID NO 143  
<211> LENGTH: 8  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 143

Ile Lys Gln Asp Gly Ser Glu Lys  
1 5

<210> SEQ ID NO 144  
<211> LENGTH: 11  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 144

Ala Arg Ala Leu Asp Tyr Tyr Gly Met Asp Val

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1 5 10

<210> SEQ ID NO 145  
<211> LENGTH: 118  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 145

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

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

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

Ala	Asn	Ile	Lys	Gln	Asp	Gly	Ser	Glu	Lys	Tyr	Tyr	Val	Asp	Ser	Val
	50						55					60			

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

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

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

Thr	Val	Thr	Val	Ser	Ser										
	115														

&lt;210&gt; SEQ ID NO 146

&lt;211&gt; LENGTH: 354

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 146

gaagtgcac	tggtgagag	cggtgagggg	cttgtccagc	ccggaggatc	gctgcggctg	60
tccgtgtcg	cgtccgggtt	cacttctcc	ggtttctgga	tgtcctgggt	cagacaggca	120
ccgggaaagg	gcctcgaatg	ggtggccaaac	atcaagcagg	atggctccga	gaagtactac	180
gtcgactccg	tgagaggccg	cttcaccatc	tccgggaca	acgccaagaa	ctcgctgtac	240
ctccaaatga	atagcctcag	ggcggaaat	actgctgtgt	attactgcgc	acgcgcctt	300
gactactacg	gcatggacgt	ctggggccaa	gggaccactg	tgaccgtgtc	tagc	354

&lt;210&gt; SEQ ID NO 147

&lt;211&gt; LENGTH: 17

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 147

Arg	Ser	Ser	Gln	Ser	Leu	Leu	Asp	Ser	Asp	Asp	Gly	Asn	Thr	Tyr	Leu
1							5					10			15

Asp

&lt;210&gt; SEQ ID NO 148

&lt;211&gt; LENGTH: 7

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<212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 148

Thr	Leu	Ser	Tyr	Arg	Ala	Ser
1						5

<210> SEQ ID NO 149  
 <211> LENGTH: 10  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 149

Thr	Gln	Arg	Leu	Glu	Phe	Pro	Ser	Ile	Thr	Tyr
1									10	
										5

<210> SEQ ID NO 150  
 <211> LENGTH: 13  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 150

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

<210> SEQ ID NO 151  
 <211> LENGTH: 3  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 151

Thr	Leu	Ser
1		

<210> SEQ ID NO 152  
 <211> LENGTH: 7  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 152

Arg	Leu	Glu	Phe	Pro	Ser	Ile
1						5

<210> SEQ ID NO 153  
 <211> LENGTH: 12  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 153

Gln Ser Leu Leu Asp Ser Asp Asp Gly Asn Thr Tyr

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1 5 10

<210> SEQ ID NO 154  
<211> LENGTH: 114  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 154

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

Glu	Pro	Ala	Ser	Ile	Ser	Cys	Arg	Ser	Ser	Gln	Ser	Leu	Leu	Asp	Ser
														20	30

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

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

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

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

Arg	Leu	Glu	Phe	Pro	Ser	Ile	Thr	Phe	Gly	Gln	Gly	Thr	Arg	Leu	Glu
												100	105	110	

Ile Lys

<210> SEQ ID NO 155  
<211> LENGTH: 342  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 155

gatatcgtga	tgacccagac	tccctgtcc	ctgcctgtga	ctccccggaga	accagccctcc	60
atttcctgcc	ggtcctccca	gtccctgctg	gacagcgacg	acggcaacac	ttacctggac	120
tggtaacttgc	agaagccggg	ccaatcgct	cgectgctga	tctataccct	gtcataccgg	180
gcctcaggag	tgcctgaccg	cttctcgga	tcagggagcg	ggaccgattt	caccctgaaa	240
atttcccggag	tggaagccga	ggacgtcgga	ctgtactact	gcacccagcg	cctcgaattc	300
ccgtcgattta	cgttggaca	gggtacccgg	cttgagatca	ag		342

<210> SEQ ID NO 156  
<211> LENGTH: 252  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 156

Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly
1														
												15		

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

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

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Ala	Asn	Ile	Lys	Gln	Asp	Gly	Ser	Glu	Lys	Tyr	Tyr	Val	Asp	Ser	Val
50				55				60							
Arg	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Ser	Leu	Tyr
65				70				75							80
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
85					90			95							
Ala	Arg	Ala	Leu	Asp	Tyr	Tyr	Gly	Met	Asp	Val	Trp	Gly	Gln	Gly	Thr
100					105				110						
Thr	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Ser		
115					120				125						
Gly	Gly	Gly	Ser	Gly	Gly	Gly	Ser	Asp	Ile	Val	Met	Thr	Gln		
130					135			140							
Thr	Pro	Leu	Ser	Leu	Pro	Val	Thr	Pro	Gly	Glu	Pro	Ala	Ser	Ile	Ser
145					150			155							160
Cys	Arg	Ser	Ser	Gln	Ser	Leu	Leu	Asp	Ser	Asp	Asp	Gly	Asn	Thr	Tyr
165					170			175							
Leu	Asp	Trp	Tyr	Leu	Gln	Lys	Pro	Gly	Gln	Ser	Pro	Arg	Leu	Ile	
180					185				190						
Tyr	Thr	Leu	Ser	Tyr	Arg	Ala	Ser	Gly	Val	Pro	Asp	Arg	Phe	Ser	Gly
195					200				205						
Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Lys	Ile	Ser	Arg	Val	Glu	Ala
210					215			220							
Glu	Asp	Val	Gly	Leu	Tyr	Tyr	Cys	Thr	Gln	Arg	Leu	Glu	Phe	Pro	Ser
225					230			235				240			
Ile	Thr	Phe	Gly	Gln	Gly	Thr	Arg	Leu	Glu	Ile	Lys				
245					250										

<210> SEQ ID NO 157  
<211> LENGTH: 756  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 157

gaagtgcac	tggggagag	cgggtggaggg	cttgcac	ccggaggatc	gctggcgctg	60
tcctgtgt	cgccgggtt	cacccatcc	ggcttctgg	tgtcctgggt	cagacaggca	120
ccggggaaagg	gcctcgaatg	ggtgccaaac	atcaagcagg	atggctccga	gaagtactac	180
gtcgactccg	tgagaggccg	cttccaccatc	tcccggacaa	acgccaagaa	ctcgctgtac	240
ctccaaatga	atagcctcag	ggcggaaat	actgctgtgt	attactgcgc	acgcgcctt	300
gactactacg	gcatggacgt	ctggggccaa	gggaccactg	tgaccgtgtc	tagcggaggc	360
ggagggttcag	ggggcggtgg	atcaggcgg	ggaggatcgg	gggggtgggg	atcggatatc	420
gtgtatgaccc	agactccccct	gtccctgcct	gtgactcccc	gagaaccaggc	ctccatttcc	480
tgccgggtct	cccactccct	gctggacago	gacgacggca	acacttacct	ggactggtag	540
ttgcagaagc	cggggcaatc	gcctcgccctg	ctgatctata	ccctgtcata	ccgggcctca	600
ggagtgccctg	accgcttctc	gggatcagggg	agcgggaccg	atttcaccct	aaaaatttcc	660
cgagtgaaag	ccgaggacgt	cggactgtac	tactgcaccc	agcgccctcg	attcccgatc	720
attacgtttg	gacagggtac	ccgggttgag	atcaag			756

<210> SEQ ID NO 158  
<211> LENGTH: 475

487

488

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<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 158

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

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

Ala Asn Ile Lys Gln Asp Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val  
50 55 60

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

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

Ala Arg Ala Leu Asp Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr

Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser

Gly Gly Gly Ser Gly Gly Gly Ser Asp Ile Val Met Thr Gln  
130 135 140

Thr	Pro	Leu	Ser	Leu	Pro	Val	Thr	Pro	Gly	Glu	Pro	Ala	Ser	Ile	Ser
145					150					155					160

Cys Arg Ser Ser Gln Ser Leu Leu Asp Ser Asp Asp Gly Asn Thr Tyr  
165 170 175

Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Arg Leu Leu Ile  
                  180                 185                 190

Tyr Thr Leu Ser Tyr Arg Ala Ser Gly Val Pro Asp Arg Phe Ser Gly  
                  195                 200                 205

Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala  
210 215 220

Glu	Asp	Val	Gly	Leu	Tyr	Tyr	Cys	Thr	Gln	Arg	Leu	Glu	Phe	Pro	Ser
225					230				235					240	

Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Thr Thr Thr Pro  
245 250 255

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu  
260 265 270

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His  
275 280 285

Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu  
290 295 300

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr  
305 310 315 320

Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe  
325 330 335

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

Phe Pro Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser

Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr

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Asn	Glu	Leu	Asn	Leu	Gly	Arg	Arg	Glu	Glu	Tyr	Asp	Val	Leu	Asp	Lys
385				390				395					400		
Arg	Arg	Gly	Arg	Asp	Pro	Glu	Met	Gly	Gly	Lys	Pro	Arg	Arg	Lys	Asn
				405				410					415		
Pro	Gln	Glu	Gly	Leu	Tyr	Asn	Glu	Leu	Gln	Lys	Asp	Lys	Met	Ala	Glu
				420				425					430		
Ala	Tyr	Ser	Glu	Ile	Gly	Met	Lys	Gly	Glu	Arg	Arg	Gly	Lys	Gly	
				435				440					445		
His	Asp	Gly	Leu	Tyr	Gln	Gly	Leu	Ser	Thr	Ala	Thr	Lys	Asp	Thr	Tyr
				450				455					460		
Asp	Ala	Leu	His	Met	Gln	Ala	Leu	Pro	Pro	Arg					
				465				470					475		

<210> SEQ ID NO 159  
<211> LENGTH: 1425  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide  
<400> SEQUENCE: 159

gaagtgcac	tggggagag	cgggtggagg	cttgcggc	ccggaggatc	gctgcggctg	60
tcctgtgt	cgtccgggtt	cacttctcc	ggcttctgga	tgtcctgggt	cagacaggca	120
ccggaaagg	gcctcgaatg	ggtgccaaac	atcaaggcgg	atggctccga	gaagtactac	180
gtcgactccg	tgagaggccg	cttccaccatc	tcccgggaca	acgccaagaa	ctcgctgtac	240
ctccaaatga	atagcctcag	ggcggaaat	actgctgtgt	attactgcgc	acgcgcctt	300
gactactacg	gcatggacgt	ctggggccaa	gggaccactg	tgaccgtgtc	tagcggaggc	360
ggagggttcag	ggggcggtgg	atcaggcgga	ggaggatcg	gggggtgggtgg	atcggatatc	420
gtgatgaccc	agactccccct	gtccctgcct	gtgactcccg	gagaaccagc	ctccatttcc	480
tgccggctct	cccagtcct	gctggacago	gacgacggca	acacttacct	ggactggtag	540
ttgcagaagc	cgggccaaatc	gcctcgctg	ctgatctata	ccctgtcata	ccgggcctca	600
ggagtgcctg	accgtttctc	gggatcagg	agcgggaccg	atttcaccc	aaaaatttcc	660
cgagtggaaag	ccgaggacgt	cgactgtac	tactgcaccc	agcgccctcg	attcccgtag	720
attacgtttg	gacagggtac	ccggcttgag	atcaagacca	ctacccagc	accgaggcca	780
cccaaaaaa	ctccattaccat	cgcctccag	cctctgtccc	tgcgtccgg	ggcatgtaga	840
cccgccatcg	gtggggccgt	gcatacccg	ggtcttgact	tgcctgcga	tatctacatt	900
tggccccc	tggctggta	ttgcgggtc	ctgctgtttt	cactcgtag	cactctttac	960
tgtaagcg	gtcggaaagaa	gctgtgtac	atcttaagc	aacccttcat	gaggctgtg	1020
caagactactc	aagaggagga	cggctgttca	tgccgggtcc	cagaggagga	ggaaggccgc	1080
tgccaaactgc	gcgtgaaatt	cagccgcgc	gcagatgtc	cagcctacca	gcagggcag	1140
aaccagactct	acaacgaact	caatcttgg	cggagagagg	agtacgacgt	gctggacaag	1200
cggagaggac	gggacccaga	aatggggcgg	aagccgcgc	gaaagaatcc	ccaagaggc	1260
ctgtacaacg	agctccaaa	ggataagatg	gcagaagct	atagcgagat	tggatgaaa	1320
ggggaaacgca	aaagaggcaa	aggccacgc	ggactgtacc	agggactcag	caccgcacc	1380
aaggacacct	atgacgctct	tcacatgcag	gccctgcgc	ctcg		1425

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<210> SEQ ID NO 160  
<211> LENGTH: 5  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 160

Ser Phe Arg Met Asn  
1 5

<210> SEQ ID NO 161  
<211> LENGTH: 17  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 161

Ser Ile Ser Ser Ser Ser Tyr Ile Tyr Tyr Ala Asp Ser Val Lys  
1 5 10 15

Gly

<210> SEQ ID NO 162  
<211> LENGTH: 9  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 162

Trp Leu Ser Tyr Tyr Gly Met Asp Val  
1 5

<210> SEQ ID NO 163  
<211> LENGTH: 7  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 163

Gly Phe Thr Phe Ser Ser Phe  
1 5

<210> SEQ ID NO 164  
<211> LENGTH: 6  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 164

Ser Ser Ser Ser Ser Tyr  
1 5

<210> SEQ ID NO 165  
<211> LENGTH: 8  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

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&lt;400&gt; SEQUENCE: 165

Gly Phe Thr Phe Ser Ser Phe Arg  
1               5

<210> SEQ ID NO 166  
<211> LENGTH: 8  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 166

Ile Ser Ser Ser Ser Ser Tyr Ile  
1               5

<210> SEQ ID NO 167  
<211> LENGTH: 11  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 167

Ala Arg Trp Leu Ser Tyr Tyr Gly Met Asp Val  
1               5                   10

<210> SEQ ID NO 168  
<211> LENGTH: 118  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 168

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

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

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

Ser Ser Ile Ser Ser Ser Ser Tyr Ile Tyr Tyr Ala Asp Ser Val  
50              55                   60

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

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

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

Thr Val Thr Val Ser Ser  
115

<210> SEQ ID NO 169  
<211> LENGTH: 354  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 169

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gaagtgcac tggtgagag cggtggaggg cttgtcaagc ccggaggatc gctgcggctg      60
tcctgtctg cgtccgggtt caccttcctcc tcgttccgcg tgaactgggt cagacaggca      120
ccggaaagg gcctcgaatg ggtgtcctca atctcatcgat cctcgctcta catctactac      180
gccgactccg tgaaaggccg ctaccatc tccgggaca acgccaagaa ctcgctgtac      240
ctccaaatga atagcctcag ggcgaaagat actgctgtgt attactgcgc acgctggctt      300
tcctactacg gcatggacgt ctggggccaa gggaccactg tgaccgtgtc tagc      354

```

```

<210> SEQ ID NO 170
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

```

<400> SEQUENCE: 170

```

Thr Leu Ser Phe Arg Ala Ser
1           5

```

```

<210> SEQ ID NO 171
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

```

<400> SEQUENCE: 171

```

Met Gln Arg Ile Gly Phe Pro Ile Thr
1           5

```

```

<210> SEQ ID NO 172
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

```

<400> SEQUENCE: 172

```

Arg Ile Gly Phe Pro Ile
1           5

```

```

<210> SEQ ID NO 173
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polypeptide

```

<400> SEQUENCE: 173

```

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

```

```

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

```

```

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

```

```

Ser Pro Gln Leu Leu Ile Tyr Thr Leu Ser Phe Arg Ala Ser Gly Val
50          55          60

```

Pro Asp Arg Phe Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys

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-continued

65	70	75	80
Ile Arg Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln			
	85	90	95

Arg Ile Gly Phe Pro Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile  
100 105 110

Lys

```
<210> SEQ ID NO 174
<211> LENGTH: 339
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide
```

<400> SEQUENCE: 174

gatatacgta tgacccagac tccccctgtcc ctgcctgtga ctcggaga accagacctcc	60
atttcctgcg ggtcctccca gtccctgtcg gacagcgacg acggcaacac ttacctggac	120
tggtaactgc agaagccggg ccaatcgct cagctgtga tctataccct gtcattccgg	180
gcctcaggag tgcctgaccg ctctctcgga tcagggagcg ggaccgattt caccctgaaa	240
attaggcgag tggaagccga ggacgtcgga gtgtactact gcatgcagcg catcggttc	300
ccgattacgt ttggacaggg taccgggtt gagatcaag	339

<210> SEQ ID NO 175  
<211> LENGTH: 251  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 175

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

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

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

Ser Ser Ile Ser Ser Ser Ser Tyr Ile Tyr Tyr Ala Asp Ser Val  
50 55 60

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

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

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

Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser  
115 120 125

Gly Gly Gly Ser Gly Gly Gly Ser Asp Ile Val Met Thr Gln  
130 135 140

Thr	Pro	Leu	Ser	Leu	Pro	Val	Thr	Pro	Gly	Glu	Pro	Ala	Ser	Ile	Ser
145					150					155					160

Cys Arg Ser Ser Gln Ser Leu Leu Asp Ser Asp Asp Gly Asn Thr Tyr  
165 170 175

Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile  
180 185 190

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-continued

Tyr Thr Leu Ser Phe Arg Ala Ser Gly Val Pro Asp Arg Phe Ser Gly  
195 200 205

Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Arg Arg Val Glu Ala  
                  210                   215                   220

Glu	Asp	Val	Gly	Val	Tyr	Tyr	Cys	Met	Gln	Arg	Ile	Gly	Phe	Pro	Ile
225					230				235						240

Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys  
245 250

```
<210> SEQ ID NO 176
<211> LENGTH: 753
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide
```

<400> SEQUENCE: 176

gaagtgcac tgggtggagag cgggtggagggg ctgttcaagc cggaggatc gctgcggctg  
tcctgtgtcg cgtccgggtt cactttctcc tcgttccgca tgaactgggt cagacaggca 120  
ccggggaaagg gcctcgaatg ggtgtcccta atctcatcg tctcgctcta catctactac 180  
gccgactccg tgaaaggccg cttcaccatc tcccgggaca acgccaagaa ctcgctgtac 240  
ctccaaatga atagcctcag ggccgaagat actgctgtgt attactgcgc acgctggctt 300  
tcctactacg gcatggacgt ctggggccaa gggaccactg tgaccgtgtc tagcggaggc 360  
ggaggttcag ggggcgggtgg atcaggcggta ggaggatcg ggggttgtgg atcggatata 420  
gtgatgaccc agactccccct gtccctgcct gtgactccccg gagaaccagc ctccatttcc 480  
tgccggctt cccagtcct gctggacagc gaeacggca acacttacct ggactggatc 540  
ttgcagaagc cgggccaatc gcctcagctg ctgatctata ccctgtcatt ccgggcctca 600  
ggagtgccctg accgcttctc gggatcggg agcgggaccc atttccccct gaaaattagg 660  
cgagtgaaag ccgaggacgt cgaggatgtac tactgcatgc agcgcatcg cttcccgatt 720  
acqtttqqac aqqqtaccq qcttqaqatc aaq 753

```
<210> SEQ ID NO 177
<211> LENGTH: 474
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide
```

<400> SEQUENCE: 177

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

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

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

Ser Ser Ile Ser Ser Ser Ser Tyr Ile Tyr Tyr Ala Asp Ser Val  
50 55 60

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

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

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-continued

Ala Arg Trp Leu Ser Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr  
 100 105 110  
 Thr Val Thr Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Ser  
 115 120 125  
 Gly Gly Gly Ser Gly Gly Ser Asp Ile Val Met Thr Gln  
 130 135 140  
 Thr Pro Leu Ser Leu Pro Val Thr Pro Gly Glu Pro Ala Ser Ile Ser  
 145 150 155 160  
 Cys Arg Ser Ser Gln Ser Leu Leu Asp Ser Asp Asp Gly Asn Thr Tyr  
 165 170 175  
 Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile  
 180 185 190  
 Tyr Thr Leu Ser Phe Arg Ala Ser Gly Val Pro Asp Arg Phe Ser Gly  
 195 200 205  
 Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Arg Arg Val Glu Ala  
 210 215 220  
 Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Arg Ile Gly Phe Pro Ile  
 225 230 235 240  
 Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Thr Thr Pro Ala  
 245 250 255  
 Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser  
 260 265 270  
 Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr  
 275 280 285  
 Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala  
 290 295 300  
 Gly Thr Cys Gly Val Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys  
 305 310 315 320  
 Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met  
 325 330 335  
 Arg Pro Val Gln Thr Thr Gln Glu Asp Gly Cys Ser Cys Arg Phe  
 340 345 350  
 Pro Glu Glu Glu Gly Cys Glu Leu Arg Val Lys Phe Ser Arg  
 355 360 365  
 Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn  
 370 375 380  
 Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg  
 385 390 395 400  
 Arg Gly Arg Asp Pro Glu Met Gly Lys Pro Arg Arg Lys Asn Pro  
 405 410 415  
 Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala  
 420 425 430  
 Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His  
 435 440 445  
 Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp  
 450 455 460  
 Ala Leu His Met Gln Ala Leu Pro Pro Arg  
 465 470

<210> SEQ ID NO 178  
 <211> LENGTH: 1422  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

-continued

## polynucleotide

<400> SEQUENCE: 178

```

gaagtgcac tggggagag cggggagggtt cttgtcaagc ccggaggatc gctggggctg      60
tcctgtgtc cgtccgggtt cacttctcc tcgttccgca tgaactgggt cagacaggca      120
ccggggaaagg gcgtcgaaatg ggtgtcccta attcatcgat ctcgtccata catctactac      180
ggcgactccg tgaaaaggccg cttcaccatc tccccggaca acgccaagaa ctgcgtgtac      240
ctccaaatga atagccttag ggcggaaatg actgctgtgt attactgcgc acgctggctt      300
tcctactacg gcatggacgt ctggggccaa gggaccactg tgaccgtgtc tagcggaggc      360
ggagggttcag ggggggggtgg atcaggcgga ggaggatcggtgggggtgg atcggatatc      420
gtgtatgaccc agactccccct gtccctgtct gtgactccccct gagaaccatc ctccattcc      480
tgccgggtctt cccagttccct gctggacago gacgacggca acacttacccctt gggactggatc      540
ttgcagaagc cggggccaaatc gcctcagctg ctgatctata ccctgtcattt ccggggccatc      600
ggagggtgtc accgcgttccctt gggatcagggg agcggggaccg atttccatctt gaaaatttgg      660
cgagtgaaatc cggaggacgtt cggaggatgtac tactgtcatgc agcgtatcggtt cttcccgatt      720
acgtttggac agggttccctt gcttgagatc aagaccacta ccccaaggacc gggccacccc      780
accccggttc ctaccatcgc ctcccgccctt ctgtccctgc gtccggaggc atgttagaccc      840
gcagctgggtt gggccgtgtca tacccgggtt ctgtacttgc cctgtcatat ctatattttgg      900
ggcccttctgg ctgggtacttgc cgggggttccctt ctgtgtatcac tctttactgt      960
aagcgcggtc ggaagaagct gctgtacatc tttaagcaac ctttcatgag gcctgtgcag      1020
actactcaag aggaggacgg ctgttcatgc cgggttccctt agaggaggaa aggccggctgc      1080
gaactgcgcg tgaaatttgc cccgcggca gatgttccatc ctttccatgc ggggcagaac      1140
cagcttctaca acgaactcaa tcttgggtcg agagaggatc acgtatgttgc ggacaagcg      1200
agaggacggg acccagaaat gggccggaaat cccgcggca gaaatccccca agagggttccctg      1260
tacaacgagc tccaaaagga taagatggca gaaggctata gcgagatgg tatgaaaggg      1320
gaacgcggaaat gggccggaaat cccgcggca gaaatccccca agagggttccctg      1380
gacacctatg acgttccatc catgcggcc ctggcccttc gg      1422

```

&lt;210&gt; SEQ ID NO 179

&lt;211&gt; LENGTH: 5

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;220&gt; FEATURE:

&lt;221&gt; NAME/KEY: MOD\_RES

&lt;222&gt; LOCATION: (1)..(1)

&lt;223&gt; OTHER INFORMATION: G or S

&lt;220&gt; FEATURE:

&lt;221&gt; NAME/KEY: MOD\_RES

&lt;222&gt; LOCATION: (3)..(3)

&lt;223&gt; OTHER INFORMATION: W or R

&lt;220&gt; FEATURE:

&lt;221&gt; NAME/KEY: MOD\_RES

&lt;222&gt; LOCATION: (5)..(5)

&lt;223&gt; OTHER INFORMATION: S or N

&lt;400&gt; SEQUENCE: 179

Xaa Phe Xaa Met Xaa

-continued

```

<210> SEQ ID NO 180
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      peptide
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: N or S
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: K or S
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Q or S
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: D or S
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: G or S
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: E or Y
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: K or I
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: V or A
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (16)..(16)
<223> OTHER INFORMATION: R or K

<400> SEQUENCE: 180

Xaa Ile Xaa Xaa Xaa Xaa Ser Xaa Xaa Tyr Tyr Xaa Asp Ser Val Xaa
1          5           10          15

Gly

```

```

<210> SEQ ID NO 181
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      peptide
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: A or W
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: D or S

<400> SEQUENCE: 181

```

```

Xaa Leu Xaa Tyr Tyr Gly Met Asp Val
1          5

```

```

<210> SEQ ID NO 182
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

```

-continued

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide  
 <220> FEATURE:  
 <221> NAME/KEY: MOD\_RES  
 <222> LOCATION: (4)..(4)  
 <223> OTHER INFORMATION: Y or F

<400> SEQUENCE: 182

Thr Leu Ser Xaa Arg Ala Ser  
 1 5

<210> SEQ ID NO 183  
 <211> LENGTH: 10  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide  
 <220> FEATURE:  
 <221> NAME/KEY: MOD\_RES  
 <222> LOCATION: (1)..(1)  
 <223> OTHER INFORMATION: T or M  
 <220> FEATURE:  
 <221> NAME/KEY: MOD\_RES  
 <222> LOCATION: (4)..(4)  
 <223> OTHER INFORMATION: L or I  
 <220> FEATURE:  
 <221> NAME/KEY: MOD\_RES  
 <222> LOCATION: (5)..(5)  
 <223> OTHER INFORMATION: E or G  
 <220> FEATURE:  
 <221> NAME/KEY: MOD\_RES  
 <222> LOCATION: (8)..(8)  
 <223> OTHER INFORMATION: S or absent

<400> SEQUENCE: 183

Xaa Gln Arg Xaa Xaa Phe Pro Xaa Ile Thr  
 1 5 10

<210> SEQ ID NO 184  
 <211> LENGTH: 7  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide  
 <220> FEATURE:  
 <221> NAME/KEY: MOD\_RES  
 <222> LOCATION: (6)..(6)  
 <223> OTHER INFORMATION: G or S

<400> SEQUENCE: 184

Gly Phe Thr Phe Ser Xaa Phe  
 1 5

<210> SEQ ID NO 185  
 <211> LENGTH: 6  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide  
 <220> FEATURE:  
 <221> NAME/KEY: MOD\_RES  
 <222> LOCATION: (1)..(1)  
 <223> OTHER INFORMATION: K or S  
 <220> FEATURE:  
 <221> NAME/KEY: MOD\_RES  
 <222> LOCATION: (2)..(2)  
 <223> OTHER INFORMATION: Q or S  
 <220> FEATURE:  
 <221> NAME/KEY: MOD\_RES  
 <222> LOCATION: (3)..(3)

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```

<223> OTHER INFORMATION: D or S
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: G or S
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: E or Y

<400> SEQUENCE: 185

```

Xaa Xaa Xaa Xaa Ser Xaa  
1                       5

```

<210> SEQ ID NO 186
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
          peptide
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: L or I
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: E or G
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: S or absent

<400> SEQUENCE: 186

```

Arg Xaa Xaa Phe Pro Xaa Ile  
1                       5

```

<210> SEQ ID NO 187
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
          peptide
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: G or S
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: W or R

<400> SEQUENCE: 187

```

Gly Phe Thr Phe Ser Xaa Phe Xaa  
1                       5

```

<210> SEQ ID NO 188
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
          peptide
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: K or S
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Q or S

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-continued

<220> FEATURE:  
<221> NAME/KEY: MOD\_RES  
<222> LOCATION: (4)..(4)  
<223> OTHER INFORMATION: D or S  
<220> FEATURE:  
<221> NAME/KEY: MOD\_RES  
<222> LOCATION: (5)..(5)  
<223> OTHER INFORMATION: G or S  
<220> FEATURE:  
<221> NAME/KEY: MOD\_RES  
<222> LOCATION: (7)..(7)  
<223> OTHER INFORMATION: E or Y  
<220> FEATURE:  
<221> NAME/KEY: MOD\_RES  
<222> LOCATION: (8)..(8)  
<223> OTHER INFORMATION: K or I

&lt;400&gt; SEQUENCE: 188

Ile Xaa Xaa Xaa Xaa Ser Xaa Xaa  
1 5

<210> SEQ ID NO 189  
<211> LENGTH: 11  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide  
<220> FEATURE:  
<221> NAME/KEY: MOD\_RES  
<222> LOCATION: (3)..(3)  
<223> OTHER INFORMATION: A or W  
<220> FEATURE:  
<221> NAME/KEY: MOD\_RES  
<222> LOCATION: (5)..(5)  
<223> OTHER INFORMATION: D or S

&lt;400&gt; SEQUENCE: 189

Ala Arg Xaa Leu Xaa Tyr Tyr Gly Met Asp Val  
1 5 10

<210> SEQ ID NO 190  
<211> LENGTH: 521  
<212> TYPE: DNA  
<213> ORGANISM: Unknown  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Unknown:  
PGK Promoter sequence

&lt;400&gt; SEQUENCE: 190

acccctcttccagccacta agccagttgc tccctgggt gacggctgca cggaggcct	60
ccgaacgtct tacgccttgt ggccgcggcc tccttgccc gggtgtatg gcgggggtgtg	120
ggccggaggcg cgtggcgcccc aaggccggc gacgagagcc ggcggggacg actcgtccgc	180
gataaccgggt gtccggtagc gccagccgcg cgacggtaac gagggacccgc gacaggcaga	240
cgcctccatg atcactctgc acgccgaagg caaatagtgc aggccgtgcg ggccttgcg	300
tcccttgaa gggctgaatc cccgcctcg tcctcgcacg ggcccccgg gtgttccat	360
cgcgcgttct agggccactg cgacgcttgc ctgcacttct tacacgctct gggtcccac	420
cgcggcgacg caaaggccct tggtgcgggt ctgcgtggcg cagggacgcg tttgggtccc	480
gacggAACCT tttccgcgtt ggggttgggg caccataaagc t	521

<210> SEQ ID NO 191  
<211> LENGTH: 221  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:

-continued

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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 191

acccctcttccagccacta agccagttgc tccctcggt gacggctgca cgcgaggcct	60
ccgaacgtct tacgccttgt ggcgcgcccc tccttgcggc ggggtgtatg gcgggggttg	120
gggcggaggg cgtggcgcccc aaggggccggc gacgagagcc ggcggggacg actcgctggc	180
gataaccggt gtccggtagc gccagcccgcg cgacggtaac g	221

<210> SEQ ID NO 192

<211> LENGTH: 324

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 192

acccctcttccagccacta agccagttgc tccctcggt gacggctgca cgcgaggcct	60
ccgaacgtct tacgccttgt ggcgcgcccc tccttgcggc ggggtgtatg gcgggggttg	120
gggcggaggg cgtggcgcccc aaggggccggc gacgagagcc ggcggggacg actcgctggc	180
gataaccggt gtccggtagc gccagcccgcg cgacggtaac gagggaccgc gacaggcaga	240
cgctcccatg atcactctgc acgccgaagg caaatagtgc aggccgtgcg gcgcttgcg	300
tcccttggaa gggctgaatc ccccg	324

<210> SEQ ID NO 193

<211> LENGTH: 422

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 193

acccctcttccagccacta agccagttgc tccctcggt gacggctgca cgcgaggcct	60
ccgaacgtct tacgccttgt ggcgcgcccc tccttgcggc ggggtgtatg gcgggggttg	120
gggcggaggg cgtggcgcccc aaggggccggc gacgagagcc ggcggggacg actcgctggc	180
gataaccggt gtccggtagc gccagcccgcg cgacggtaac gagggaccgc gacaggcaga	240
cgctcccatg atcactctgc acgccgaagg caaatagtgc aggccgtgcg gcgcttgcg	300
tcccttggaa gggctgaatc cccgccttgt ctttcgcagc ggccccccgg gtgtccat	360
cggccgttctt aggcccactg cgacgcttgc ctgcacttct tacacgtctt gggccat	420
cg	422

<210> SEQ ID NO 194

<400> SEQUENCE: 194

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<210> SEQ ID NO 195

<400> SEQUENCE: 195

000

<210> SEQ ID NO 196

-continued

&lt;400&gt; SEQUENCE: 196

000

&lt;210&gt; SEQ ID NO 197

&lt;400&gt; SEQUENCE: 197

000

&lt;210&gt; SEQ ID NO 198

&lt;211&gt; LENGTH: 118

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 198

acccctctct ccagccacta agccagttgc tccctcggtt gacggctgca cgcgaggcct 60

ccgaacgtct tacgccttgtt ggcgcgcggc tccttgccc gggtgtatg gcgggggtg 118

&lt;210&gt; SEQ ID NO 199

&lt;211&gt; LENGTH: 63

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

&lt;400&gt; SEQUENCE: 199

atggccctcc ctgtcacccgc cctgctgctt ccgcgtggctc ttctgctcca cgccgctcgg 60

ccc 63

&lt;210&gt; SEQ ID NO 200

&lt;211&gt; LENGTH: 239

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 200

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly  
1 5 10 15Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Ala Leu Ser Asn His  
20 25 30Gly Met Ser Trp Val Arg Arg Ala Pro Gly Lys Gly Leu Glu Trp Val  
35 40 45Ser Gly Ile Val Tyr Ser Gly Ser Thr Tyr Ala Ala Ser Val Lys  
50 55 60Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg Asn Thr Leu Tyr Leu  
65 70 75 80Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Ile Tyr Tyr Cys Ser  
85 90 95Ala His Gly Gly Glu Ser Asp Val Trp Gly Gln Gly Thr Thr Val Thr  
100 105 110Val Ser Ser Ala Ser Gly Gly Ser Gly Gly Ser Gly  
115 120 125Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser  
130 135 140

-continued

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser  
145 150 155 160

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

Lys Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser  
180 185 190

Arg Phe Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser  
195 200 205

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr  
210 215 220

Ser Thr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys  
225 230 235

&lt;210&gt; SEQ ID NO 201

&lt;211&gt; LENGTH: 717

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 201

gaagtgtcaat	tgggtgaaatc	agggggagga	cttgcgcgc	ctggaggatc	gctgagactg	60
tcatgtcccg	tgtccggctt	tgcctgtcc	aaccacggga	tgtcctgggt	ccgcccgcgc	120
cctggaaagg	gcctcgaatg	ggtgtcggtt	attgtgtaca	gcggtagcac	ctactatgcc	180
gcatccgtga	aggggagatt	caccatcago	cgggacaact	ccaggaacac	tctgtacctc	240
caaataatt	cgctgaggcc	agaggacact	gccatctact	actgctccgc	gcatggcgga	300
gagtccgacg	tctggggaca	ggggaccacc	gtgaccgtgt	ctagcgcgtc	cgccggaggc	360
ggcagcgggg	gtgggtgttc	agggggcggc	ggatcggaca	tccagctcac	ccagtccccg	420
agctcgtgt	ccgcctccgt	gggagatcg	gtcaccatca	cgtgcgcgc	cagccagtcg	480
atttcctct	acctgaactg	gtaccaacag	aagcccgaa	aagcccccga	gcttctcatc	540
tacgcccct	cgagcctgca	gtcaggagtg	ccctcacgg	tctccggctc	cggttccgg	600
actgatttca	ccctgaccat	ttcctccctg	caaccggagg	acttgcgtac	ttactactgc	660
cagcagtcgt	actccacccc	ctacacttgc	ggacaaggca	ccaagggtcga	aatcaag	717

&lt;210&gt; SEQ ID NO 202

&lt;211&gt; LENGTH: 69

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 202

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

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

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

Trp	Ala	Pro	Leu	Ala	Gly	Thr	Cys	Gly	Val	Leu	Leu	Ser	Leu	Val
	50				55			60						

Ile	Thr	Leu	Tyr	Cys
	65			

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<210> SEQ ID NO 203  
<211> LENGTH: 207  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 203

```
accactaccc cagcacccgag gccacccacc ccggcttcta ccatgcctc ccagectctg      60
tccctgegtc cggaggcatg tagaccgcga gctgggtgggg ccgtgcatac ccgggggttt      120
gacttcgcct gcgatatctta catttggcc cctctggctg gtacttgccg ggtctgtctg      180
ctttcaactcg tgatcaactct ttactgt                                207
```

<210> SEQ ID NO 204  
<211> LENGTH: 126  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 204

```
aagcgcggtc ggaagaagct gctgtacata tttaaagcaac ctttcatgag gcctgtgcag      60
actactcaag aggaggacgg ctgttcatgc cggttcccag aggaggagga aggccggctgc      120
gaactg                                         126
```

<210> SEQ ID NO 205  
<211> LENGTH: 336  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 205

```
cgcgtgaaat tcagccgcag cgcagatgtt ccagccattacc agcaggggca gaaccagctc      60
tacaacgaac tcaatcttgg tcggagagag gagtacgacg tgctggacaa gcggagagga      120
cgggaccagg aaatgggcgg gaagccgcgc agaaagaatc cccaagaggg cctgtacaac      180
gagctccaaa aggataagat ggcagaagcc tatagcgaga ttggatgaa agggaaacgc      240
agaagaggca aaggccacga cggactgtac cagggactca gcaccgcac caaggacacc      300
tatgacgctc ttcacatgca ggccctgccc cctcggt                                336
```

<210> SEQ ID NO 206  
<211> LENGTH: 3  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 206

Gly Ser Gly  
1

<210> SEQ ID NO 207  
<211> LENGTH: 9  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence

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-continued

<220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

&lt;400&gt; SEQUENCE: 207

ggaagcgga

9

<210> SEQ ID NO 208  
 <211> LENGTH: 19  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 208

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

Pro Gly Pro

<210> SEQ ID NO 209  
 <211> LENGTH: 57  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

&lt;400&gt; SEQUENCE: 209

gctactaact tcagcctgct gaagcaggct ggagacgtgg aggagaaccc tggacct 57

<210> SEQ ID NO 210  
 <211> LENGTH: 63  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

&lt;400&gt; SEQUENCE: 210

atggccttac cagtgaccgc cttgtccctg ccgctggct tgctgtcca cgccgccagg	60
ccg	63

<210> SEQ ID NO 211  
 <211> LENGTH: 242  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 211

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

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

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile	45	
35	40	45

Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly	60	
50	55	60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro	80		
65	70	75	80

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr

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85	90	95	
Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Ser			
100	105	110	
Gly Gly Gly Ser Gly Gly Gly Ser Gln Val Gln Leu Gln Glu			
115	120	125	
Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys			
130	135	140	
Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg			
145	150	155	160
Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly Val Ile Trp Gly Ser			
165	170	175	
Glu Thr Thr Tyr Tyr Gln Ser Ser Leu Lys Ser Arg Val Thr Ile Ser			
180	185	190	
Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr			
195	200	205	
Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly			
210	215	220	
Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val			
225	230	235	240
Ser Ser			

<210> SEQ ID NO 212  
<211> LENGTH: 726  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 212

gaaattgtga tgaccaggc	acccgcact cttagcctt	cacccggta gcgcgcaacc	60
ctgtcttgca gagcctccca	agacatctca aaatacccta	atggtatca acagaagccc	120
ggacaggcgc ctcgccttct	gatctaccac accagccgc	tccattctgg aatccctgcc	180
aggttcagcg gtagcggatc	tgggaccgac tacaccctca	ctatcagctc actgcagcca	240
gaggacttcg ctgtctat	tttctgtcagcaa gggAACACCC	tgcctacac ctttggacag	300
ggcaccaagc tcgagattaa	agggtggaggt ggcagcggag	gagggtggtc cggcggtgga	360
ggaagccagg tccaa	cttccactcca agaaagcgg	ccgggttctt gtaagccatc agaaactctt	420
tcactgactt gtactgtgag	cgagggtgtct ctccccgatt	acgggggtgc ttggatcaga	480
cagccacccg ggaagggtct	ggaatggatt ggagtgattt	ggggctctga gactactac	540
taccaatcat ccctcaagtc	acgcgtcacc atctcaaagg	acaactctaa gaatcagg	600
tcactgaaac tgcatactgt	gaccgcagcc gacaccgc	tgtactattg cgctaagcat	660
tactattatg gcgggagcta	cgcaatggat tactggggac	agggtactct ggtcaccgt	720
tccagc			726

<210> SEQ ID NO 213  
<211> LENGTH: 207  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 213

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accacgacgc cagcgccgca accacccaaca ccggcgccca ccatcgctc gcagccccgt	60
tccctgegcc cagaggcgctg ccggccageg gggggggggc cagtgcacac gagggggctg	120
gacttcgcct gtgatatacta catctggcgg cccttggccg ggacttgtgg ggtccttctc	180
ctgtcactgg ttatcacccct ttactgc	207

<210> SEQ ID NO 214  
<211> LENGTH: 1000  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 214

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu	
1 5 10 15	

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

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe	
35 40 45	

Thr Phe Ser Ser Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys	
50 55 60	

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

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser	
85 90 95	

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr	
100 105 110	

Ala Val Tyr Tyr Cys Ala Arg Arg Glu Trp Trp Gly Glu Ser Trp Leu	
115 120 125	

Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly	
130 135 140	

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Gly	
145 150 155 160	

Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser	
165 170 175	

Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser	
180 185 190	

Ser Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu	
195 200 205	

Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe	
210 215 220	

Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu	
225 230 235 240	

Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr	
245 250 255	

Pro Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Thr Thr Thr	
260 265 270	

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

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

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

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Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu  
                   325                  330                  335  
  
 Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro  
                   340                  345                  350  
  
 Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys  
                   355                  360                  365  
  
 Arg Phe Pro Glu Glu Glu Gly Cys Glu Leu Arg Val Lys Phe  
                   370                  375                  380  
  
 Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu  
                   385                  390                  395                  400  
  
 Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp  
                   405                  410                  415  
  
 Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys  
                   420                  425                  430  
  
 Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala  
                   435                  440                  445  
  
 Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys  
                   450                  455                  460  
  
 Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr  
                   465                  470                  475                  480  
  
 Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg Gly Ser Gly Ala  
                   485                  490                  495  
  
 Thr Asn Phe Ser Leu Leu Lys Gln Ala Gly Asp Val Glu Glu Asn Pro  
                   500                  505                  510  
  
 Gly Pro Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu  
                   515                  520                  525  
  
 Leu Leu His Ala Ala Arg Pro Glu Ile Val Met Thr Gln Ser Pro Ala  
                   530                  535                  540  
  
 Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala  
                   545                  550                  555                  560  
  
 Ser Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly  
                   565                  570                  575  
  
 Gln Ala Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly  
                   580                  585                  590  
  
 Ile Pro Ala Arg Phe Ser Gly Ser Gly Thr Asp Tyr Thr Leu  
                   595                  600                  605  
  
 Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln  
                   610                  615                  620  
  
 Gln Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu  
                   625                  630                  635                  640  
  
 Ile Lys Gly Gly Gly Ser Gly Gly Ser Gly Gly Gly Gly  
                   645                  650                  655  
  
 Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser  
                   660                  665                  670  
  
 Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp  
                   675                  680                  685  
  
 Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp  
                   690                  695                  700  
  
 Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Gln Ser Ser Leu  
                   705                  710                  715                  720  
  
 Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln Val Ser  
                   725                  730                  735  
  
 Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys

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740	745	750
Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly		
755	760	765
Gln Gly Thr Leu Val Thr Val Ser Ser Thr Thr Pro Ala Pro Arg		
770	775	780
Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg		
785	790	795
800		
Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly		
805	810	815
Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr		
820	825	830
Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg		
835	840	845
Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro		
850	855	860
Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu		
865	870	875
880		
Glu Glu Glu Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala		
885	890	895
Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu		
900	905	910
Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly		
915	920	925
Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu		
930	935	940
Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser		
945	950	955
960		
Glu Ile Gly Met Lys Gly Glu Arg Arg Gly Lys Gly His Asp Gly		
965	970	975
Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu		
980	985	990
His Met Gln Ala Leu Pro Pro Arg		
995	1000	

<210> SEQ ID NO 215  
<211> LENGTH: 3000  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 215

atggccctcc ctgtcacgc cctgctgctt ccgctggctc ttctgtccca cgccgctcg	60
ccccgaagtgc agttgctgga gtcaggcggaa ggactgggtc agcccgaggagg atcgcttcgc	120
tttagagctgcg cagcctcagg ctttacacctc tcctcctacg ccatgtccctg ggtcagacag	180
gctcccgaaa agggactgga atgggtgtcc gccattagcg gttccggcgg aagcaattac	240
tatgccgact ctgtgaagggg ccgcgttcaact atctcccgaaa acaactccaa gaacaccctg	300
tatctccaaa tgaattccct gagggccgaa gataccgcgg tggactactg cgcttagacgg	360
gagtgggtggg gagaaagctg gctgttcgac tactggggac agggcactct cgtgactgtg	420
tcctccggtg gtgggtggatc ggggggtgtt ggttcggcgg gaggaggatc tggaggagga	480
gggtcgacata ttcaaattgac tcagtcggcc tcctccctct ccgcctccgt gggagatcgc	540

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gtcacgatca cgtgcagggc cagccagago atctccagct acctgaactg gtaccagcg	600
aagccaggaa aggacccgaa gctctgatc taegccgcta gtcgcgtca gtccggcgtc	660
ccttcacggt tctcgggatc gggctcaggo accgacttca ccctgaccat tagcagctg	720
cagccggagg acttcgcgac atactactgt cagcagtcat actccacccc tctgaccctc	780
ggccaaggaa ccaaagtgg aatcaagacc actaccccg caccgaggcc accccacccg	840
gctcctacca tcgcctccca gcctctgtcc ctgcgtccgg aggcattgttag accccgacgt	900
ggtggggccg tgcataacccg gggcttgcac ttgcctgcg atatctacat ttggccct	960
ctggctggta cttgcggggt cctgcgtgtt tcactcgatc tcactcttta ctgtaaagcgc	1020
ggtcggaaga agctgctgtt catcttaag caacccttca tgaggcctgt gcagactact	1080
caagaggagg acggctgttc atgcgggttc ccagaggagg aggaaggccg ctgcgactg	1140
cgcgtgaaat tcagccgcag cgccatgtct ccagcctacc agcaggggca gaaccagctc	1200
tacaacgaac tcaatcttgc tcggagagag gagtacgacg tgctggacaa gcggagagga	1260
cgggaccacccg aaatgggcgg gaagccgcgc agaaagaatc cccaaaggaggg cctgtacaac	1320
gagctccaaa aggataagat ggcagaagcc tatagcgaga ttggatgaa agggaaacgc	1380
agaagaggca aaggccacga cggactgtac cagggactca gcaccgcac caaggacacc	1440
tatgacgctc ttcacatgca ggccctgccc cctcggggaa gcggagctac taacttcagc	1500
ctgctgaagc aggctggaga cgtggaggag aaccctggac ctatggccctt accagtgacc	1560
gccttgctcc tgccgctggc cttgcgtgtc cacggcccca ggccggaaat tgtgatgacc	1620
cagtcacccg ccactcttag ctttcaccc ggtgagcgcc caaccctgtc ttgcagagcc	1680
tcccaagaca tctcaaaata ccttaattgg tatcaacaga agccggaca ggctcctcgc	1740
cttctgtatc accacaccag cgggtccat tctggaatcc ctgcgggtt cagcggtac	1800
ggatctggga ccgactacac cctcaactatc agctcaactgc agccagagga cttcgctgtc	1860
tatttcgttc agcaaggaa caccctgccc tacaccttg gacaggcac caagctcgag	1920
attnaagggtg gaggtggcag cggaggaggt gggccggcg gtggaggaag ccaggtccaa	1980
ctccaaagaaa ggggaccggg tcttgtgaag ccatcagaaa ctctttact gacttgtact	2040
gtgagcggag tgtctctccc cgattacggg gtgtcttggc tcagacagcc accggggaaag	2100
ggtctggaaat ggattggagt gatgggggc tctgagacta cttactacca atcatccctc	2160
aagtcaacgc tcaccatctc aaaggacaac tctaagaatc aggtgtcaact gaaactgtca	2220
tctgtgaccg cagccgacac cgccgtgtac tattgcgtcta agcattacta ttatggccgg	2280
agctacgcaa tggattactg gggacagggt actctggtca ccgtgtccag caccacgacg	2340
ccagcgcgc gaccaccaac accggccccc accatcgctc cgcagccccct gtccctgcgc	2400
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tgtgatatact acatctgggc gcccttggcc gggacttggc gggcttcttct cctgtcaact	2520
gttatcaccc ttactgcaa acggggcaga aagaaactcc tgtatataatt caaacaacca	2580
tttatgagac cagtcacaaac tactcaagag gaagatggct gtagctgcgcg atttccagaa	2640
gaagaagaag gaggatgtga actgagagtg aagttcagca ggagcgcaga cgccccccgc	2700
taccagcagg gccagaacca gctctataac gagctcaatc taggacgaag agaggagtag	2760
gatgtttgg acaagagacg tggccgggac cctgagatgg gggaaagcc gagaaggaaag	2820
aaccctcagg aaggcctgtt caatgaactg cagaaagata agatggcga ggcctacagt	2880
gagattggga tgaaaggcga ggcggggagg ggcaggggc acgtggcct ttaccagggt	2940

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ctcagtagccaccaagga cacctacgac gcccgttcaca tgcaggccct gccccctcg 3000

<210> SEQ ID NO 216  
<211> LENGTH: 1001  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 216

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu			
1	5	10	15
His Ala Ala Arg Pro Gln Val Gln Leu Gln Glu Ser Gly Gly Val			
20	25	30	
Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe			
35	40	45	
Thr Phe Ser Ser Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys			
50	55	60	
Gly Leu Glu Trp Val Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr			
65	70	75	80
Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser			
85	90	95	
Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr			
100	105	110	
Ala Val Tyr Tyr Cys Gly Gly Ser Gly Tyr Ala Leu His Asp Asp Tyr			
115	120	125	
Tyr Gly Leu Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser			
130	135	140	
Gly Gly Gly Ser Gly Gly Ser Gly Ser Gly Gly Ser Gln			
145	150	155	160
Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser			
165	170	175	
Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Tyr Asn			
180	185	190	
Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met			
195	200	205	
Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe Ser			
210	215	220	
Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln			
225	230	235	240
Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser Ser			
245	250	255	
Thr Leu Tyr Val Phe Gly Ser Gly Thr Lys Val Thr Val Leu Thr Thr			
260	265	270	
Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln			
275	280	285	
Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala			
290	295	300	
Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala			
305	310	315	320
Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr			
325	330	335	
Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln			
340	345	350	

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Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser  
 355 360 365  
 Cys Arg Phe Pro Glu Glu Glu Gly Cys Glu Leu Arg Val Lys  
 370 375 380  
 Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln  
 385 390 395 400  
 Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu  
 405 410 415  
 Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg  
 420 425 430  
 Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met  
 435 440 445  
 Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly  
 450 455 460  
 Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp  
 465 470 475 480  
 Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg Gly Ser Gly  
 485 490 495  
 Ala Thr Asn Phe Ser Leu Leu Lys Gln Ala Gly Asp Val Glu Glu Asn  
 500 505 510  
 Pro Gly Pro Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala  
 515 520 525  
 Leu Leu Leu His Ala Ala Arg Pro Glu Ile Val Met Thr Gln Ser Pro  
 530 535 540  
 Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg  
 545 550 555 560  
 Ala Ser Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro  
 565 570 575  
 Gly Gln Ala Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser  
 580 585 590  
 Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr  
 595 600 605  
 Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys  
 610 615 620  
 Gln Gln Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu  
 625 630 635 640  
 Glu Ile Lys Gly Gly Ser Gly Gly Ser Gly Ser Gly Gly  
 645 650 655  
 Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro  
 660 665 670  
 Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro  
 675 680 685  
 Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu  
 690 695 700  
 Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Gln Ser Ser  
 705 710 715 720  
 Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln Val  
 725 730 735  
 Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr  
 740 745 750  
 Cys Ala Lys His Tyr Tyr Tyr Gly Ser Tyr Ala Met Asp Tyr Trp  
 755 760 765

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Gly Gln Gly Thr Leu Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro  
770 775 780

Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu  
785 790 795 800

Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg  
805 810 815

Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly  
820 825 830

Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys  
835 840 845

Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg  
850 855 860

Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro  
865 870 875 880

Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser  
885 890 895

Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu  
900 905 910

Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg  
915 920 925

Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln  
930 935 940

Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr  
945 950 955 960

Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp  
965 970 975

Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala  
980 985 990

Leu His Met Gln Ala Leu Pro Pro Arg  
995 1000

<210> SEQ ID NO 217  
<211> LENGTH: 3003  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 217

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cccccaagtgc agctgcagga atccgggtggc ggagtcgtgc agcctggaaag gagcctgaga     120
ctctcatcgcg ccgcgtcagg gttcaccttt tcctcctacg ggatgcattg ggtcagacag     180
ccccccggaa agggactcga atgggtggct gtgatcagct acgacggctc caacaagtac     240
tacggccact ccgtgaaaagg ccggttcaact atctcccggg acaactccaa gaacacgtg     300
tatctgcaaa tgaattcaact gcgcgcggag gataccgttg tgtaactactg cggtggctcc    360
ggttacgccc tgcacgatga ctattacggc cttgacgtct ggggccaggg aaccctcgta    420
actgtgtcca gcggtggagg aggttcgggc ggaggaggat caggaggggg tggatcgcag    480
agcgcactga ctcagccggc atccgtgtcc ggttagcccg gacagtgcgtt taccatctcc    540
tgtaccggca cttccctccga cgtggggagg tacaactacg tgctgtggta ccagcagcac    600
ccagggaaagg cccctaagtt gatgatctac gatgtgtcaa accgcccgtc tggagtctcc    660
aacccggttct ccggctccaa gtccggcaac accgcccagcc tgaccattag cgggctgcaa    720

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gccgaggatg aggccgacta ctactgctcg agctacacat cctcagcac cctctacgtg	780
ttcggctcg ggactaaggt caccgtctg accactaccc cagcaccgag gccacccacc	840
ccggctcta ccatacgctc ccagcctctg tccctgcgtc cggaggcatg tagacccgca	900
gctgggtggg ccgtgcatac cgggggtttt gacttcgcct gcgatatcta catttggcc	960
cctctggctg gtacttgctg ggtctgtctg ctttcactcg tgatcactct ttactgtaa	1020
cgcggctgga agaagctgct gtacatctt aagcaaccct tcatacgaggc tgtcagact	1080
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ctgcgcgtga aattcagccg cagcgcagat gctccagccct accagcaggc gcagaaccag	1200
ctctacaacg aactcaatct tggtcggaga gaggagtacg acgtgtcgaa caagcggaga	1260
ggacgggacc cagaaaatggg cgggaagccg cgcagaaaaga atccccaaaa gggcctgtac	1320
aacgagctcc aaaaggataa gatggcagaa gcctatagcg agattggat gaaagggaa	1380
cgcagaagag gcaaaggcca cgacggactg taccaggcgc tcagcaccgc caccaaggac	1440
acotatgacg ctcttacat gcaggccctg ccgcctcggt gaagcggagc tactaacttc	1500
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acogccttgc tctgtccgct ggccttgctg ctccacgccc ccagggcggaa aattgtatg	1620
acccagtcac cggccactct tagectttca cccggtgagc ggcacccct gtcttgacaa	1680
gcctcccaag acatctcaaa atacctaata tggtatcaac agaageccgg acaggctcct	1740
cgccttgc tctaccacac cagccggctc cattctggaa tccctgcac gttcagcggt	1800
agcggatctg ggaccgacta caccctcaat atcagctcac tgcageccaga ggacttcgct	1860
gtctattct gtcagcaagg gaacaccctg ccctacacat ttggacaggg caccaagctc	1920
gagattaaag gtggaggtgg cagcggagga ggtgggtccg ggggtggagg aagccaggtc	1980
caactccaag aaagcggacc gggcttgcg aagccatcg aaactcttc actgacttgt	2040
actgtgacg gagtgtctct ccccgattac ggggtgtctt ggatcagaca gcccacgggg	2100
aagggtctgg aatggattgg agtggattgg ggctctgaga ctacttacta ccaatcatcc	2160
ctcaagtcac ggttcacccat ctcaaaggac aactctaaga atcagggtgc actgaaactg	2220
tcatctgtga ccgcagccga caceggctgt tactattgc ctaagcatta ctattatggc	2280
gggagctacg caatggatta ctggggacag ggtactctgg tcaccgtgtc cagcaccacg	2340
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cgtgcgggcc agcggcgcccc ggccgcagtgc acacgagggg gctggacttc	2460
gcctgtata tctacatctg ggcccccctt gcccggactt gtggggtcct tctctgtca	2520
ctgggttatca cccttactg caaacggggc agaaagaaac tcctgtatata attcaaacaa	2580
ccatttatga gaccagtaca aactactcaa gaggaagatg gctgttagctg ccgatttcca	2640
gaagaagaag aaggaggatg tgaactgaga gtgaagttca gcaggagcgc agacgcccc	2700
gcgttaccacg agggccagaa ccagctctat aacgagctca atcttaggacg aagagaggag	2760
tagatgtttt tggacaagag acgtggccgg gaccctgaga tggggggaaa gcccggaaagg	2820
aagaaccctc aggaaggccct gtacaatgaa ctgcagaaag ataagatggc ggaggccctac	2880
agtgagattg ggtgaaagg cgagcggccgg agggggcaagg ggcacgatgg cctttaccag	2940
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cgc	3003

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<210> SEQ ID NO 218  
 <211> LENGTH: 1002  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 218

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu  
1 5 10 15

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

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe  
35 40 45

Thr Phe Ser Ser Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys  
50 55 60

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

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser  
85 90 95

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr  
100 105 110

Ala Val Tyr Tyr Cys Ala Arg Arg Glu Trp Val Pro Tyr Asp Val Ser  
115 120 125

Trp Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser  
130 135 140

Gly Gly Gly Ser Gly Gly Ser Gly Gly Gly Ser Gly Gly Ser Gly  
145 150 155 160

Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser  
165 170 175

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser  
180 185 190

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

Lys Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser  
210 215 220

Arg Phe Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser  
225 230 235 240

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr  
245 250 255

Ser Thr Pro Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Thr  
260 265 270

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

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

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

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

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

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

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Ser Cys Arg Phe Pro Glu Glu Glu Gly Gly Cys Glu Leu Arg Val  
 370 375 380  
 Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn  
 385 390 395 400  
 Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val  
 405 410 415  
 Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg  
 420 425 430  
 Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys  
 435 440 445  
 Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg  
 450 455 460  
 Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys  
 465 470 475 480  
 Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg Gly Ser  
 485 490 495  
 Gly Ala Thr Asn Phe Ser Leu Leu Lys Gln Ala Gly Asp Val Glu Glu  
 500 505 510  
 Asn Pro Gly Pro Met Ala Leu Pro Val Thr Ala Leu Leu Pro Leu  
 515 520 525  
 Ala Leu Leu Leu His Ala Ala Arg Pro Glu Ile Val Met Thr Gln Ser  
 530 535 540  
 Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys  
 545 550 555 560  
 Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys  
 565 570 575  
 Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His  
 580 585 590  
 Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr  
 595 600 605  
 Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe  
 610 615 620  
 Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys  
 625 630 635 640  
 Leu Glu Ile Lys Gly Gly Ser Gly Gly Gly Ser Gly Gly  
 645 650 655  
 Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys  
 660 665 670  
 Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu  
 675 680 685  
 Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu  
 690 695 700  
 Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Gln Ser  
 705 710 715 720  
 Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln  
 725 730 735  
 Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr  
 740 745 750  
 Tyr Cys Ala Lys His Tyr Tyr Gly Ser Tyr Ala Met Asp Tyr  
 755 760 765  
 Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Thr Thr Thr Pro Ala  
 770 775 780

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Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser  
 785 790 795 800  
 Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr  
 805 810 815  
 Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala  
 820 825 830  
 Gly Thr Cys Gly Val Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys  
 835 840 845  
 Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met  
 850 855 860  
 Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe  
 865 870 875 880  
 Pro Glu Glu Glu Gly Cys Glu Leu Arg Val Lys Phe Ser Arg  
 885 890 895  
 Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn  
 900 905 910  
 Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg  
 915 920 925  
 Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro  
 930 935 940  
 Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala  
 945 950 955 960  
 Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His  
 965 970 975  
 Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp  
 980 985 990  
 Ala Leu His Met Gln Ala Leu Pro Pro Arg  
 995 1000

<210> SEQ ID NO 219  
 <211> LENGTH: 3006  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 polynucleotide

<400> SEQUENCE: 219

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cccgaaagtgc	agttgtggaa	gtcaggcgga	ggactgggtc	agccccggagg	atcgcttcgc	120
ttgagctgcg	cagcctcagg	ctttaccttc	tcctcctacg	ccatgtcctg	ggtcagacag	180
gctcccgaaa	agggactggaa	atgggtgtcc	gccattagcg	gttccggccgg	aagcacttac	240
tatgccact	ctgtgaaggg	ccgcttcaact	atctcccgaa	acaactccaa	gaacacctcg	300
tatctccaaa	tgaattccct	gagggccgaa	gataccgcgg	tgtactactg	cgctagacgg	360
gagtgggtgc	cctacgatgt	cagctggta	ttcgactact	ggggacagagg	cactctcg	420
actgtgtctt	ccgggtggtg	tggatcgaaaa	ggtgtgggtt	cgccgcggagg	aggatctgaa	480
ggaggaggg	cgacattca	aatgacttag	tcccgatccc	ccctctccgc	ctccgtggaa	540
gatcgcgtca	cgatcacgt	caggccaga	cagagcatct	ccagctacct	gaactggta	600
cagcagaagc	caggaaaggc	accgaagtc	ctgatctacg	ccgctagctc	gctgcagtc	660
ggcgtccctt	cacgggtctc	gggatcgaaa	tcaggcaccc	atccaccc	gaccattac	720
agcctgcagc	cgaggactt	cgcgacatac	tactgtcagc	agtctatactc	caccctctg	780

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gcagctggtg gggccgtgca taccgggggt cttgacttcg cctgcgatat ctacatttg	960
gcccccttgtt ctgggtacttg cggggtcctg ctgtttcac tcgtgtatcac tctttactgt	1020
aagcgcggtc ggaagaagct gctgtacato tttaagcaac cttcatgag gcctgtcag	1080
actactcaag aggaggacgg ctgttcatgc cggttcccg aggaggagga aggccggctgc	1140
gaactgcgcg tgaaatttag ccgcagcgcgca gatgctccag cctaccagca gggcagaac	1200
cagctctaca acgaactcaa tcttggtcg agagaggagt acgacgtgct ggacaagcgg	1260
agaggacggg acccagaaat gggcgaaaag ccgcgcagaa agaatccca agagggcctg	1320
tacaacgcgc tccaaaagga taatgtggca gaagcctata gcgagatttg tatgaaagg	1380
gaacgcagaa gaggcaaaagg ccacgcggc ctgttccagg gactcagcac cgccaccaag	1440
gacacctatg acgctttca catgcaggcc ctgcgcctc ggggaagcgg agctactaac	1500
ttcagcgtgc tgaagcaggc tggagacgtg gaggagaacc ctggacctat ggccttacca	1560
gtgaccgcct tgctcctgca gctggccttg ctgttccacg ccgcgcaggcc ggaaattgtg	1620
atgacccagt caccgcac tcttagcctt tcacccggtg agcgcgcac cctgtcttg	1680
agagcctccc aagacatctc aaaatacctt aattggatc aacagaagcc cggacaggct	1740
cctcgccctc tgatctacca caccagccgg ctccattctg gaatccctgc caggttcagc	1800
ggttagcggat ctgggaccga ctacacccctc actatcagtc cactgcagcc agaggactc	1860
gctgtctatt tctgtcagca agggAACACC ctgcctaca cttttggaca gggcaccaag	1920
ctcgagatta aagggtggagg tggcagcggc ggaggtgggt ccggcggtgg aggaagccag	1980
gtccaactcc aagaaaacgg accgggtctt gtgaagccat cagaaactct ttcactgact	2040
tgtactgtga gcggagtgta tctcccgat tacgggtgtt cttggatcag acagccaccc	2100
ggaaagggtc tggaaatggat tggagtgatt tggggctctg agactactta ctaccaatca	2160
tccctcaagt cacgcgtcac catctcaaag gacaactcta agaatcaggt gtcactgaaa	2220
ctgtcatctg tgaccgcagc cgacacccgc gtgtactatt gcgtctagca ttactattat	2280
ggcgccggact acgcaatggc ttactggggc cagggtactc tggtcaccgt gtccagcacc	2340
acgacgcggc cggccgcgacc accaacaccc ggcgcacca tcgcgtcgca gcccgtc	2400
ctgcgcctcagg aggccgtgccg gccagcggcgg gggggcgcag tgcacacccgg ggggctggac	2460
ttcgcctgtg atatctacat ctggggcccc ttggccgggg cttgtgggggt cttctcctg	2520
tcaactggta tcaccctta ctgcaaacgg ggcagaaaaga aactcctgtat tatattcaaa	2580
caaccattta tgagaccagt acaaactact caagaggaag atggctgttag ctggccattt	2640
ccagaagaag aagaaggagg atgtgaactg agagtgaagt tcagcaggag cgcagacgcc	2700
cccgcgtaacc acgaggccca gaaccagctc tataacgcgc tcaatctagg acgaagagag	2760
gagtaacgtat ttttggacaa gagacgtggc cgggaccctg agatgggggg aaagccgaga	2820
aggaagaacc ctcaggaagg cctgtacaat gaaactgcaga aagataagat ggccggaggcc	2880
tacagtgaga ttgggtatgaa aggccggcgc cggagggggca aggggcacga tggccttac	2940
cagggtctca gtacagccac caaggacacc tacgacgccc ttcacatgca ggcctgccc	3000
cctcgc	3006

<210> SEQ ID NO 220  
<211> LENGTH: 991

-continued

<212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 220

Met	Ala	Leu	Pro	Val	Thr	Ala	Leu	Leu	Leu	Pro	Leu	Ala	Leu	Leu
1														
														15

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

Val	Gln	Pro	Gly	Gly	Ser	Leu	Arg	Leu	Ser	Cys	Ala	Val	Ser	Gly	Phe
															45
35								40							

Ala	Leu	Ser	Asn	His	Gly	Met	Ser	Trp	Val	Arg	Arg	Ala	Pro	Gly	Lys
															60
50							55								

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

Ala	Ala	Ser	Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Arg
															95
85							90								

Asn	Thr	Leu	Tyr	Leu	Gln	Met	Asn	Ser	Leu	Arg	Pro	Glu	Asp	Thr	Ala
															110
100							105								

Ile	Tyr	Tyr	Cys	Ser	Ala	His	Gly	Gly	Glu	Ser	Asp	Val	Trp	Gly	Gln
							115	120	125						

Gly	Thr	Thr	Val	Thr	Val	Ser	Ser	Ala	Ser	Gly	Gly	Gly	Gly	Ser	Gly
															140
130							135								

Gly	Gly	Ser	Gly	Gly	Gly	Ser	Asp	Ile	Gln	Leu	Thr	Gln	Ser	
							145	150	155	160				

Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly	Asp	Arg	Val	Thr	Ile	Thr	Cys
							165	170	175						

Arg	Ala	Ser	Gln	Ser	Ile	Ser	Ser	Tyr	Leu	Asn	Trp	Tyr	Gln	Gln	Lys
								180	185	190					

Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile	Tyr	Ala	Ala	Ser	Ser	Leu	Gln
							195	200		205					

Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly	Ser	Gly	Thr	Asp	Phe	
							210	215	220					

Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro	Glu	Asp	Phe	Ala	Thr	Tyr	Tyr
							225	230	235	240					

Cys	Gln	Gln	Ser	Tyr	Ser	Thr	Pro	Tyr	Thr	Phe	Gly	Gln	Gly	Thr	Lys
							245	250	255						

Val	Glu	Ile	Lys	Thr	Thr	Pro	Ala	Pro	Arg	Pro	Pro	Thr	Pro	Ala	
							260	265	270						

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

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

Asp	Ile	Tyr	Ile	Trp	Ala	Pro	Leu	Ala	Gly	Thr	Cys	Gly	Val	Leu	Leu
							305	310	315	320					

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

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

Glu	Glu	Asp	Gly	Cys	Ser	Cys	Arg	Phe	Phe	Pro	Glu	Glu	Glu	Gly	Gly
							355	360	365						

Cys	Glu	Leu	Arg	Val	Lys	Phe	Ser	Arg	Ser	Ala	Asp	Ala	Pro	Ala	Tyr
							370	375	380						

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Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg  
 385                   390                   395                   400  
 Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met  
 405                   410                   415  
 Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu  
 420                   425                   430  
 Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys  
 435                   440                   445  
 Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu  
 450                   455                   460  
 Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu  
 465                   470                   475                   480  
 Pro Pro Arg Gly Ser Gly Ala Thr Asn Phe Ser Leu Leu Lys Gln Ala  
 485                   490                   495  
 Gly Asp Val Glu Glu Asn Pro Gly Pro Met Ala Leu Pro Val Thr Ala  
 500                   505                   510  
 Leu Leu Leu Pro Leu Ala Leu Leu His Ala Ala Arg Pro Glu Ile  
 515                   520                   525  
 Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg  
 530                   535                   540  
 Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu Asn  
 545                   550                   555                   560  
 Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr His  
 565                   570                   575  
 Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly  
 580                   585                   590  
 Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp  
 595                   600                   605  
 Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr Phe  
 610                   615                   620  
 Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Ser Gly Gly  
 625                   630                   635                   640  
 Gly Gly Ser Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly  
 645                   650                   655  
 Pro Gly Leu Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val  
 660                   665                   670  
 Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro  
 675                   680                   685  
 Pro Gly Lys Gly Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr  
 690                   695                   700  
 Thr Tyr Tyr Gln Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp  
 705                   710                   715                   720  
 Asn Ser Lys Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala  
 725                   730                   735  
 Asp Thr Ala Val Tyr Tyr Cys Ala Lys His Tyr Tyr Gly Gly Ser  
 740                   745                   750  
 Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser  
 755                   760                   765  
 Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala  
 770                   775                   780  
 Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly  
 785                   790                   795                   800

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Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile  
805 810 815

Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Ser Leu Val  
820 825 830

Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe  
835 840 845

Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly  
850 855 860

Cys Ser Cys Arg Phe Pro Glu Glu Glu Gly Gly Cys Glu Leu Arg  
865 870 875 880

Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gln  
885 890 895

Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp  
900 905 910

Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro  
915 920 925

Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp  
930 935 940

Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg  
945 950 955 960

Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr  
965 970 975

Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg  
980 985 990

<210> SEQ ID NO 221  
<211> LENGTH: 2973  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 221

atggccctcc	ctgtcacccgc	cctgtgtcctt	ccgctggctc	ttctgttcca	cgccgctcg	60
ccccgaagtgc	aatttgttgg	atcaggggaa	ggacttgtgc	agcctggagg	atcgctgaga	120
ctgtcatgtg	ccgtgtccgg	ctttgccctg	tccaaaccacg	ggatgtccctg	ggtccgcgc	180
gcgcctggaa	agggcctcga	atgggtgtcg	ggtattgtgt	acagcggtag	cacctactat	240
ggcgcatccg	tgaaggggag	attcaccatc	agccggacca	actccagggaa	cactctgtac	300
ctccaaatga	attcgctgag	gccagaggac	actgccatct	actactgctc	cgcgcatggc	360
ggagagtcgg	acgtctgggg	acaggggacc	accgtgaccg	tgtctagcgc	gtccggcgga	420
ggcggcagcg	gggggtgtgg	ttcagggggg	ggcggatcgg	acatccagct	cacccagtc	480
ccgagctcgc	tgtccgcctc	cgtggggat	cgggtcacc	tcacgtgcgc	cgccagccag	540
tcgatttctt	cctacctgaa	ctggtagccaa	cagaagcccg	gaaaagcccc	gaagcttctc	600
atctacgcgc	cctcgagcc	gcagtcagga	gtgccctcac	ggttctccgg	ctccgggttcc	660
gttactgtt	tcaccctgac	catttctcc	ctgcaaccgg	aggacttgc	tacttactac	720
tgcgcgcgt	cgtactccac	cccctacact	ttcggacaag	gcaccaaggt	cgaaatcaag	780
accactaccc	cagcaccgag	gccacccacc	ccggctctca	ccatcgcc	ccagcctctg	840
tccctgcgtc	cgaggccatg	tagacccgca	gctgggtgggg	ccgtgcatac	ccgggggtt	900
gacttcgcct	gcgatatcta	catttggggcc	cctctggctg	gtacttgccg	ggtcctgctg	960

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ctttcaactcg tgatcactct ttactgtaaag cgccggcgaa agaagctgct gtacatctt	1020
aaggcaaccct tcatgaggcc tttgcagact actcaagagg aggacggctg ttcatgcgg	1080
ttccccagagg aggaggaagg cggctgcgaa ctgcgcgtga aattcagccg cagcgcagat	1140
gctccagcc accagcaggg gcagaaccag ctctacaacg aactcaatct tggtcggaga	1200
gaggagtagc acgtgttggaa caaaggaa ggcggggacc cagaaatggg cggggagccg	1260
cgcagaaaga atccccaaaga ggcccgttac aacgagctcc aaaaggataa gatggcagaa	1320
gcctatacg agattggat gaaaggggaa cgcagaagag gcaaaggcca cgacggactg	1380
taccaggcgc tcagcaccgc caccaggac acctatgtac ctcttcacat gcaggccctg	1440
ccgcctcggg gaagcggagc tactaactt acgcgtgtac agcaggctgg agacgtggag	1500
gagaaccctg gacatgttgc cttaccagtgc accgccttgc tcttgcgcgc ggccttgc	1560
ctccacgcgc ccaggccgaa aattgtgtat acccagtac ccgcactct tagccttca	1620
cccggtgagc ggcacccct gtcttgacaa gcctcccaag acatctcaaa atacctaata	1680
tggtatcaac agaagcccg acaggctctt cgccttctga tctaccacac cagccggctc	1740
cattctggaa tccctgccag gttcagcggt agcggatctg ggaccgacta caccctcact	1800
atcagctcac tgcagccaga ggacttcgt gtctatttct gtcagcaagg gaacaccctg	1860
ccctacacct ttggacaggg caccaagctc gagattaaag gtggagggtgg cagcggagga	1920
gggtgggtccg ggggtggagg aagccaggtc caactccaaag aaagcggacc gggcttgc	1980
aagccatcg aaactcttc actgacttgt actgtgagcg gagtgtctct ccccgattac	2040
gggggtgtttt ggatcagaca gccaccgggg aagggtctgg aatggattgg agtggattgg	2100
ggctctgaga ctacttacta ccaatcatcc ctcaagtac gcgtcaccat ctcaaaggac	2160
aactctaaga atcagggtgc actgaaactg tcatctgtac ccgcagccga caccgcgtg	2220
tactattgcg ctaagcatta ctattatggc gggagctacg caatggatta ctggggacag	2280
ggtaactctgg tcaccgtgtc cagcaccacg acgccagcgc cgcgaccacc aacaccggcg	2340
ccaccatcg cgtcgagcc cctgtccctg cgcccgagg cgtccggcc agcggccggg	2400
ggcgcgatgc acacgagggg gctggacttgc gcctgtataa tctacatctg ggcgccttg	2460
ggccggactt gtggggctt tctctgtca ctgggtatca cccttactg caaacggggc	2520
agaaagaaac tcctgtatata attcaaacaa ccatttataa gaccagtaca aactactcaa	2580
gaggaagatg gctgttagctg ccgatttcca gaagaagaag aaggaggatg tgaactgaga	2640
gtgaagttca gcaggagcgc agacgcccc gcgttaccagg agggccagaa ccagcttat	2700
aacgagctca atcttaggacg aagagaggag tacatgtttt tggacaagag acgtggccgg	2760
gaccctgaga tggggggaaa gccgagaagg aagaaccctc aggaaggcct gtacaatgaa	2820
ctgcagaaag ataagatggc ggaggctac agtgagattg ggtgaaagg cgagcgcgg	2880
aggggcaagg ggcacatgg ccttaccag ggtctcagta cagccaccaa ggacacctac	2940
gacgccccttc acatgcaggc cctgccccct cgc	2973

<210> SEQ ID NO 222  
 <211> LENGTH: 991  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 222

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**557**

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Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu  
 1 5 10 15  
 His Ala Ala Arg Pro Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu  
 20 25 30  
 Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln  
 35 40 45  
 Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala  
 50 55 60  
 Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro  
 65 70 75 80  
 Ala Arg Phe Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile  
 85 90 95  
 Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly  
 100 105 110  
 Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys  
 115 120 125  
 Gly Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Ser Gln  
 130 135 140  
 Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr  
 145 150 155 160  
 Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly  
 165 170 175  
 Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly  
 180 185 190  
 Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Gln Ser Ser Leu Lys Ser  
 195 200 205  
 Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys  
 210 215 220  
 Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys  
 225 230 235 240  
 His Tyr Tyr Tyr Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly  
 245 250 255  
 Thr Leu Val Thr Val Ser Ser Thr Thr Pro Ala Pro Arg Pro Pro  
 260 265 270  
 Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu  
 275 280 285  
 Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp  
 290 295 300  
 Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly  
 305 310 315 320  
 Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg  
 325 330 335  
 Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln  
 340 345 350  
 Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu  
 355 360 365  
 Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala  
 370 375 380  
 Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu  
 385 390 395 400  
 Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp  
 405 410 415  
 Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu

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**559****560**

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420	425	430
Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile		
435	440	445
Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr		
450	455	460
Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met		
465	470	475
Gln Ala Leu Pro Pro Arg Gly Ser Gly Ala Thr Asn Phe Ser Leu Leu		
485	490	495
Lys Gln Ala Gly Asp Val Glu Glu Asn Pro Gly Pro Met Ala Leu Pro		
500	505	510
Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu His Ala Ala Arg		
515	520	525
Pro Glu Val Gln Leu Val Glu Ser Gly Gly Leu Val Gln Pro Gly		
530	535	540
Gly Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Ala Leu Ser Asn		
545	550	555
His Gly Met Ser Trp Val Arg Arg Ala Pro Gly Lys Gly Leu Glu Trp		
565	570	575
Val Ser Gly Ile Val Tyr Ser Gly Ser Thr Tyr Tyr Ala Ala Ser Val		
580	585	590
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg Asn Thr Leu Tyr		
595	600	605
Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Ile Tyr Tyr Cys		
610	615	620
Ser Ala His Gly Gly Glu Ser Asp Val Trp Gly Gln Gly Thr Thr Val		
625	630	635
Thr Val Ser Ser Ala Ser Gly Gly Ser Gly Gly Gly Ser		
645	650	655
Gly Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu		
660	665	670
Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln		
675	680	685
Ser Ile Ser Ser Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala		
690	695	700
Pro Lys Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro		
705	710	715
Ser Arg Phe Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile		
725	730	735
Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser		
740	745	750
Tyr Ser Thr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys		
755	760	765
Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala		
770	775	780
Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly		
785	790	795
Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile		
805	810	815
Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Ser Leu Val		
820	825	830
Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe		
835	840	845

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**561****562**

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Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly  
850 855 860

Cys Ser Cys Arg Phe Pro Glu Glu Glu Gly Cys Glu Leu Arg  
865 870 875 880

Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gln  
885 890 895

Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp  
900 905 910

Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Lys Pro  
915 920 925

Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp  
930 935 940

Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg  
945 950 955 960

Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr  
965 970 975

Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg  
980 985 990

<210> SEQ ID NO 223  
<211> LENGTH: 2973  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 223

atggccttac cagtgaccgc	60
cttgctcccg ccgctggcct tgctgctcca	120
cggaaattg ttagtaccca gtcacccgcc actcttagcc	180
tttcacccgg tgagegcgca	240
accctgtctt gcagagcctc ccaagacata tcaaaatacc	300
ttaattggta tcaacagaag	360
cccgacagg ctccctcgcc tctgatctac cacaccagcc	420
ggctccatcc tggaatccct	480
gccaggttca gggtagccgg atctgggacc	540
gactacaccc tcaactatcag ctcactgcag	600
ccagaggact tcgctgtcta tttctgtcag	660
caaggaaaca ccctgeccctt cacctttggaa	720
caggcgcacca agctcgagat taaagggtgg	780
gggtggcagcg gaggagggtgg gtccggcggt	840
ggaggaagcc aggtccaact ccaagaaago ggaccgggtc	900
tttgtgaagcc atcagaaact	960
cttctactga ctgtactgt gacggagtg tctctcccc	1020
attacgggggt gtcttgatc	1080
tttggggctc tgagactact	1140
catccctcaa gtcacgcgtc accatctcaa aggacaactc	1200
taagaatcgtgtgtactga aactgtcatc	
tgtgacccgc gccgacaccg ccgtgtacta ttgcgccta	
gattactggg gacagggtac tctgggtcacc	
gtgtccagca ccacgacgccc agcgcgcgca	
ccaccaacac cggcgcccac catcgctcg	
cagccccgtt ccctgcgcggc agaggcgtgc	
cggccagcgg cggggggcgc agtgcacacg	
agggggctgg acttcgcctg tgatatctac atctggggcgc	
ccttggccgg gactttgtggg	
gtccttcctcc tttttttttt tactaccctt tactgcaaac	
ggggcggaaa gaaactctgt	
tatataattca aacaaccatt tatgagacca gtacaaacta	
ctcaagagga agatggctgt	
agctgcccgtt ttccagaaga agaagaagga ggatgtgaac	
tgagagtggaa gttcagcagg	
agcgcagacg ccccccgcgtt ccagcaggcc cagaaccacg	
tctataacgac gctcaatcta	

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**563****564**

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ggacgaagag aggagtacga tgggggaccc tgagatgggg 1260
ggaaagccga gaaggaagaa ccctcaggaa ggccgttaca atgaactgca gaaagataag 1320
atggcgagg cctacagtga gattggatg aaaggcgagc gcccgggggg caaggggcac 1380
gatggcctt accagggtct cagtagcc accaaggaca cttacgacgc cttcacatg 1440
caggccctgc cccctcgccg aageggagct actaactca gcctgtgaa gcaggctgga 1500
gacgtggagg agaaccctgg acatatggcc ctccctgtca cccctgtct gctcccgctg 1560
gtcttcgtc tccacgccc tcggccgaa gtcaattgg tggaaatcagg gggaggactt 1620
gtgcagecctg gaggatcgct gagactgtca tgtggcgtgt cccgcgttc cctgtccaac 1680
cacggatgt cctgggtccg ccgcgcgcct ggaaaggccc tcgaatgggt gtgggtatt 1740
gtgtacagcg gtagcaccta ctatgccca tccgtgaagg ggagattcac catagccgg 1800
gacaactcca ggaacactct gtaccccaa atgaattcgc tgaggccaga ggacactgcc 1860
atctactact gtcggcgca tggcgagag tccgacgtct ggggacaggg gaccaccgt 1920
accgtgtcta cgccgtccgg cggaggccgc agccgggggtg gtgggttccgg gggccggca 1980
tcggacatcc agtcacccca gtcccgagc tcgtgtccg cccctgtgg agatccggc 2040
accatcacgt gcccgcgcag ccagtcgatt tcctccatcc tgaactggta ccaacagaag 2100
ccccggaaaag ccccgaaagct tctcatctac gcccgcctca gcctgcagtc aggagtgc 2160
tcacgggtct ccggctccgg ttccggtaact gatccatcc tcggatccatcc 2220
ccggaggact tcgctactta ctactgccag cagtcgtact ccacccctta cacttcgg 2280
caaggccacca aggtcgaaat caagaccact accccagcac cgaggccacc ccccccggct 2340
cctaccatcg ccccccggcc tctgtccctg cgtccggagg catgtagacc cgcagctgg 2400
ggggccgtgc atacccgggg tcttgacttc gcctgcgata tctacatttgc gggccctctg 2460
gctggtaactt gccccggctt gctgcttca ctcgtatca ctctttactg taagccgg 2520
cgaaagaagc tgctgtacat cttaagcaa cccttcatgaa ggccgtgtca gactactcaa 2580
gaggaggacg gctgttcatg ccgggtccca gaggaggagg aaggccggctg cgaactgcgc 2640
gtgaaattca gcccgcgcgc agatgttca gcctaccagg agggccagaa ccagctctac 2700
aacgaactca atcttggtcg gagagaggag tacgacgtgc tggacaagcg gagaggacgg 2760
gaccccgaaaa tggccggaa gcccgcgcaga aagaatcccc aagaggccct gtacaacgg 2820
ctccaaaagg ataagatggc agaagcttat agcgagattt gatgaaagg ggaacgcaga 2880
agaggcaaag gccacgcacgg actgttaccag ggactcagca ccggccaccaa ggacacctat 2940
gacgcttcc acatgcagggc cctggccctt cgg 2973

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<210> SEQ ID NO 224  
<211> LENGTH: 492  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 224

Glu	Val	Gln	Leu
1	5	10	15

Ser	Leu	Arg	Leu
20	25	30	

Ala	Met	Ser	Trp
35	40	45	

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-continued

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val  
 50 55 60  
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr  
 65 70 75 80  
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95  
 Ala Arg Arg Glu Trp Trp Gly Glu Ser Trp Leu Phe Asp Tyr Trp Gly  
 100 105 110  
 Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly  
 115 120 125  
 Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Asp Ile Gln  
 130 135 140  
 Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val  
 145 150 155 160  
 Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn Trp  
 165 170 175  
 Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala  
 180 185 190  
 Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser  
 195 200 205  
 Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe  
 210 215 220  
 Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Leu Thr Phe Gly  
 225 230 235 240  
 Gln Gly Thr Lys Val Glu Ile Lys Thr Thr Pro Ala Pro Arg Pro  
 245 250 255  
 Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro  
 260 265 270  
 Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu  
 275 280 285  
 Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys  
 290 295 300  
 Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly  
 305 310 315 320  
 Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val  
 325 330 335  
 Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu  
 340 345 350  
 Glu Glu Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp  
 355 360 365  
 Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn  
 370 375 380  
 Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg  
 385 390 395 400  
 Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly  
 405 410 415  
 Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu  
 420 425 430  
 Ile Gly Met Lys Gly Glu Arg Arg Gly Lys Gly His Asp Gly Leu  
 435 440 445  
 Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His  
 450 455 460

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-continued

Met Gln Ala Leu Pro Pro Arg Gly Ser Gly Ala Thr Asn Phe Ser Leu  
 465                   470                   475                   480

Leu Lys Gln Ala Gly Asp Val Glu Glu Asn Pro Gly  
 485                   490

<210> SEQ ID NO 225  
 <211> LENGTH: 465  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 225

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

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

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile  
 35                   40                   45

Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly  
 50                   55                   60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro  
 65                   70                   75                   80

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr  
 85                   90                   95

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

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

Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys  
 130               135               140

Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg  
 145               150               155               160

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

Glu Thr Thr Tyr Tyr Gln Ser Ser Leu Lys Ser Arg Val Thr Ile Ser  
 180               185               190

Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr  
 195               200               205

Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly  
 210               215               220

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

Ser Ser Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr  
 245               250               255

Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala  
 260               265               270

Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile  
 275               280               285

Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser  
 290               295               300

Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr  
 305               310               315               320

Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu  
 325               330               335

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-continued

Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Gly Gly Cys Glu  
 340 345 350

Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln  
 355 360 365

Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu  
 370 375 380

Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly  
 385 390 395 400

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

Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu  
 420 425 430

Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr  
 435 440 445

Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro  
 450 455 460

Arg  
 465

<210> SEQ ID NO 226  
 <211> LENGTH: 493  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 226

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

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

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

Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val  
 50 55 60

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

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

Gly Gly Ser Gly Tyr Ala Leu His Asp Asp Tyr Tyr Gly Leu Asp Val  
 100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser  
 115 120 125

Gly Gly Gly Ser Gly Gly Ser Gln Ser Ala Leu Thr Gln  
 130 135 140

Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys  
 145 150 155 160

Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr  
 165 170 175

Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Asp Val Ser  
 180 185 190

Asn Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly  
 195 200 205

Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala

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210	215	220
Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser Ser Thr	Leu Tyr Val Phe	
225 230 235	240	
Gly Ser Gly Thr Lys Val Thr Val Leu Thr Thr Pro	Ala Pro Arg	
245 250 255		
Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro	Leu Ser Leu Arg	
260 265 270		
Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val	His Thr Arg Gly	
275 280 285		
Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro	Leu Ala Gly Thr	
290 295 300		
Cys Gly Val Leu Leu Ser Leu Val Ile Thr Leu Tyr	Cys Lys Arg	
305 310 315 320		
Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro	Phe Met Arg Pro	
325 330 335		
Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys	Arg Phe Pro Glu	
340 345 350		
Glu Glu Glu Gly Cys Glu Leu Arg Val Lys Phe Ser	Arg Ser Ala	
355 360 365		
Asp Ala Pro Ala Tyr Gln Gln Gln Asn Gln Leu Tyr	Asn Glu Leu	
370 375 380		
Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp	Lys Arg Arg Gly	
385 390 395 400		
Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys	Asn Pro Gln Glu	
405 410 415		
Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala	Glu Ala Tyr Ser	
420 425 430		
Glu Ile Gly Met Lys Gly Glu Arg Arg Gly Lys His	Asp Gly	
435 440 445		
Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr	Tyr Asp Ala Leu	
450 455 460		
His Met Gln Ala Leu Pro Pro Arg Gly Ser Gly Ala	Thr Asn Phe Ser	
465 470 475 480		
Leu Leu Lys Gln Ala Gly Asp Val Glu Glu Asn Pro	Gly	
485 490		

<210> SEQ ID NO 227  
<211> LENGTH: 494  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 227

Glu Val Gln Leu Leu Glu Ser Gly Gly	Leu Val Gln Pro Gly Gly	
1 5 10 15		
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr	Phe Ser Ser Tyr	
20 25 30		
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly	Leu Glu Trp Val	
35 40 45		
Ser Ala Ile Ser Gly Ser Gly Ser Thr Tyr Tyr Ala	Asp Ser Val	
50 55 60		
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys	Asn Thr Leu Tyr	
65 70 75 80		

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Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
   85                   90                   95  
  
 Ala Arg Arg Glu Trp Val Pro Tyr Asp Val Ser Trp Tyr Phe Asp Tyr  
   100               105               110  
  
 Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser  
   115               120               125  
  
 Gly Gly Gly Ser Gly Gly Ser Gly Gly Gly Ser Asp  
   130               135               140  
  
 Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp  
   145               150               155               160  
  
 Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu  
   165               170               175  
  
 Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr  
   180               185               190  
  
 Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser  
   195               200               205  
  
 Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu  
   210               215               220  
  
 Asp Phe Ala Thr Tyr Tyr Cys Gln Ser Tyr Ser Thr Pro Leu Thr  
   225               230               235               240  
  
 Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Thr Thr Thr Pro Ala Pro  
   245               250               255  
  
 Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu  
   260               265               270  
  
 Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg  
   275               280               285  
  
 Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly  
   290               295               300  
  
 Thr Cys Gly Val Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys  
   305               310               315               320  
  
 Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg  
   325               330               335  
  
 Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro  
   340               345               350  
  
 Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser  
   355               360               365  
  
 Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu  
   370               375               380  
  
 Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg  
   385               390               395               400  
  
 Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln  
   405               410               415  
  
 Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr  
   420               425               430  
  
 Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp  
   435               440               445  
  
 Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala  
   450               455               460  
  
 Leu His Met Gln Ala Leu Pro Pro Arg Gly Ser Gly Ala Thr Asn Phe  
   465               470               475               480  
  
 Ser Leu Leu Lys Gln Ala Gly Asp Val Glu Glu Asn Pro Gly  
   485               490

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-continued

<210> SEQ ID NO 228  
<211> LENGTH: 483  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 228

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

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Ala Leu Ser Asn His  
20              25              30

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

Ser Gly Ile Val Tyr Ser Gly Ser Thr Tyr Tyr Ala Ala Ser Val Lys  
50              55              60

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

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

Ala His Gly Glu Ser Asp Val Trp Gly Gln Gly Thr Thr Val Thr  
100            105            110

Val Ser Ser Ala Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly  
115            120            125

Gly Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser  
130            135            140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser  
145            150            155            160

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

Lys Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser  
180            185            190

Arg Phe Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser  
195            200            205

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr  
210            215            220

Ser Thr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Thr  
225            230            235            240

Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser  
245            250            255

Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly  
260            265            270

Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp  
275            280            285

Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile  
290            295            300

Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys  
305            310            315            320

Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys  
325            330            335

Ser Cys Arg Phe Pro Glu Glu Glu Gly Gly Cys Glu Leu Arg Val  
340            345            350

Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn  
355            360            365

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-continued

Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val  
 370                   375                   380

Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg  
 385                   390                   395                   400

Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys  
 405                   410                   415

Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg  
 420                   425                   430

Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys  
 435                   440                   445

Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg Gly Ser  
 450                   455                   460

Gly Ala Thr Asn Phe Ser Leu Leu Lys Gln Ala Gly Asp Val Glu Glu  
 465                   470                   475                   480

Asn Pro Gly

<210> SEQ ID NO 229

<211> LENGTH: 486

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 229

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

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

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile  
 35                   40                   45

Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly  
 50                   55                   60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro  
 65                   70                   75                   80

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr  
 85                   90                   95

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

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

Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys  
 130                   135                   140

Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg  
 145                   150                   155                   160

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

Glu Thr Thr Tyr Tyr Gln Ser Ser Leu Lys Ser Arg Val Thr Ile Ser  
 180                   185                   190

Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr  
 195                   200                   205

Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly  
 210                   215                   220

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

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**579****580**

-continued

Ser Ser Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr  
245 250 255

Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala  
260 265 270

Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile  
275 280 285

Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Ser  
290 295 300

Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr  
305 310 315 320

Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu  
325 330 335

Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Gly Cys Glu  
340 345 350

Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln  
355 360 365

Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu  
370 375 380

Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly  
385 390 395 400

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

Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu  
420 425 430

Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr  
435 440 445

Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro  
450 455 460

Arg Gly Ser Gly Ala Thr Asn Phe Ser Leu Leu Lys Gln Ala Gly Asp  
465 470 475 480

Val Glu Glu Asn Pro Gly  
485

<210> SEQ ID NO 230  
<211> LENGTH: 462  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 230

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

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Ala Leu Ser Asn His  
20 25 30

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

Ser Gly Ile Val Tyr Ser Gly Ser Thr Tyr Tyr Ala Ala Ser Val Lys  
50 55 60

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

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

Ala His Gly Gly Glu Ser Asp Val Trp Gly Gln Gly Thr Thr Val Thr  
100 105 110

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Val Ser Ser Ala Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly  
115 120 125

Gly Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser  
130 135 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser  
145 150 155 160

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

Lys Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser  
180 185 190

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser  
195 200 205

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr  
210 215 220

Ser Thr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Thr  
225 230 235 240

Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser  
245 250 255

Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly  
260 265 270

Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp  
275 280 285

Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile  
290 295 300

Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys  
305 310 315 320

Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys  
325 330 335

Ser Cys Arg Phe Pro Glu Glu Glu Gly Gly Cys Glu Leu Arg Val  
340 345 350

Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn  
355 360 365

Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val  
370 375 380

Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg  
385 390 395 400

Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys  
405 410 415

Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg  
420 425 430

Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys  
435 440 445

Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg  
450 455 460

<210> SEQ ID NO 231  
<211> LENGTH: 5  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide  
<400> SEQUENCE: 231  
Asn His Gly Met Ser

-continued

1 5

<210> SEQ ID NO 232  
<211> LENGTH: 16  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 232

Gly	Ile	Val	Tyr	Ser	Gly	Ser	Thr	Tyr	Tyr	Ala	Ala	Ser	Val	Lys	Gly
1			5				10						15		

<210> SEQ ID NO 233  
<211> LENGTH: 7  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 233

His	Gly	Gly	Glu	Ser	Asp	Val
1			5			

<210> SEQ ID NO 234  
<211> LENGTH: 7  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 234

Gly	Phe	Ala	Leu	Ser	Asn	His
1			5			

<210> SEQ ID NO 235  
<211> LENGTH: 5  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 235

Val	Tyr	Ser	Gly	Ser
1			5	

<210> SEQ ID NO 236  
<211> LENGTH: 8  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 236

Gly	Phe	Ala	Leu	Ser	Asn	His	Gly
1				5			

<210> SEQ ID NO 237  
<211> LENGTH: 7  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

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## peptide

&lt;400&gt; SEQUENCE: 237

Ile Val Tyr Ser Gly Ser Thr  
1 5

&lt;210&gt; SEQ ID NO 238

&lt;211&gt; LENGTH: 9

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 238

Ser Ala His Gly Gly Glu Ser Asp Val  
1 5

&lt;210&gt; SEQ ID NO 239

&lt;211&gt; LENGTH: 115

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 239

Glu Val Gln Leu Val Glu Ser Gly Gly Leu Val Gln Pro Gly Gly  
1 5 10 15Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Ala Leu Ser Asn His  
20 25 30Gly Met Ser Trp Val Arg Arg Ala Pro Gly Lys Gly Leu Glu Trp Val  
35 40 45Ser Gly Ile Val Tyr Ser Gly Ser Thr Tyr Tyr Ala Ala Ser Val Lys  
50 55 60Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg Asn Thr Leu Tyr Leu  
65 70 75 80Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Ile Tyr Tyr Cys Ser  
85 90 95Ala His Gly Gly Glu Ser Asp Val Trp Gly Gln Gly Thr Thr Val Thr  
100 105 110Val Ser Ser  
115

&lt;210&gt; SEQ ID NO 240

&lt;211&gt; LENGTH: 9

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 240

Gln Gln Ser Tyr Ser Thr Pro Tyr Thr  
1 5

&lt;210&gt; SEQ ID NO 241

&lt;211&gt; LENGTH: 6

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

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&lt;400&gt; SEQUENCE: 241

Ser Tyr Ser Thr Pro Tyr  
1 5

<210> SEQ ID NO 242  
<211> LENGTH: 107  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 242

Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly  
1 5 10 15Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr  
20 25 30Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile  
35 40 45Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly  
50 55 60Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro  
65 70 75 80Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Tyr  
85 90 95Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys  
100 105

<210> SEQ ID NO 243  
<211> LENGTH: 17  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 243

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

Ser

<210> SEQ ID NO 244  
<211> LENGTH: 10  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 244

Gly Val Ser Leu Pro Asp Tyr Gly Val Ser  
1 5 10

<210> SEQ ID NO 245  
<211> LENGTH: 16  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 245

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Gln Ser Ser Leu Lys Ser

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1                          5                          10

```
<210> SEQ ID NO 246
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      peptide
```

<400> SEQUENCE: 246

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr  
1 5 10

<210> SEQ ID NO 247

```
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial
      peptide
```

1000 SEQUENCE: 217

Arg Ala Ser Gin Asp Ile Ser Lys Tyr Leu Asn  
1 5 10

<210> SEQ ID NO 248

```
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      peptide
```

<400> SEQUENCE: 248

His Thr Ser Arg Leu His Ser  
1 5

<210> SEQ ID NO 249

```
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide
```

<400> SEQUENCE: 249

Gln Gln Gly Asn Thr Leu Pro Tyr Thr  
1 5

<210> SEQ ID NO 250

```
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
    polypeptide
```

100 - 2000000000 - 200

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu

Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile  
25 10 15

Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Gln Ser Ser Leu Lys

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50 55 60

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

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala  
 85 90 95

Lys His Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln  
 100 105 110

Gly Thr Leu Val Thr Val Ser Ser  
 115 120

&lt;210&gt; SEQ ID NO 251

&lt;211&gt; LENGTH: 107

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 251

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

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

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile  
 35 40 45

Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly  
 50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro  
 65 70 75 80

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr  
 85 90 95

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

&lt;210&gt; SEQ ID NO 252

&lt;211&gt; LENGTH: 63

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

&lt;400&gt; SEQUENCE: 252

atggccctcc ctgtcaccgc tctgttgctg ccgcattgctc tgctgtccca cgcaagcgca 60

ccg 63

&lt;210&gt; SEQ ID NO 253

&lt;211&gt; LENGTH: 747

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 253

caggtacaat tgcaggagtc tggaggcggt gtggtgcaac ccgggtcgcaag cttgcgcctg 60

agtttgtgctg cgtctggatt tacatttca tcttacggaa tgcattgggt acgccaggca 120

ccggggaaag gccttgaatg ggtggctgta atttcatacg atggttccaa caaatactat 180

gctgactcag tcaagggtcg atttacaatt agtcgggaca actccaagaa cacccttat 240

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cttcaaatga attcccttag	agcagaggat acggcggtct	attactgtgg tggcagttgt	300
tatgcacttc atgatgatta	ctatggcttg gatgtctggg	ggcaaggac gcttgtaact	360
gtatcctctg gtgggtgtgg	tagtgggtggg ggaggctccg	gcccgtggccg ctctcaatct	420
gctctgactc aaccagcaag	cgtatcaggg tcaccgggac	agagtattac cataagttgc	480
acggggacct ctagcgatgt	aggggggtat aattatgtat	cttggtatca acaacacccc	540
ggaaagcccc ctaaattgtat	gatctacgac gtgagcaatc	gacccatgtgg cgtatcaaat	600
cgttctctg gtagcaagag	tggaaatacg gctgtccat	ctattagccg attgcaagca	660
gaagatgagg ccgattacta	ctgcagctcc tatactagct	cttctacatt gtacgtctt	720
gggagcggaa caaaagtaac	agtactc		747

<210> SEQ ID NO 254				
<211> LENGTH: 207				
<212> TYPE: DNA				
<213> ORGANISM: Artificial Sequence				
<220> FEATURE:				
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide				
<400> SEQUENCE: 254				
acaacaacac ctgccccgag	accgcctaca ccagccccga	ctattgccag ccagcctctg	60	
agcctcaggc ctgaggcctg	taggcccgcga	gcggggccggcg	cagttcatac acggggcttg	120
gatttcgctt gtgatattta	tattttggct	ccttggcg	ggacatgtgg cgtgctgctt	180
ctgtcacttg ttattacact	gtactgt		207	

<210> SEQ ID NO 255				
<211> LENGTH: 126				
<212> TYPE: DNA				
<213> ORGANISM: Artificial Sequence				
<220> FEATURE:				
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide				
<400> SEQUENCE: 255				
aaacgcgggc gaaaaaaatt	gctgtatatt ttaagcagc	catttatgag gcccgttcag	60	
acgacgcagg aggaggacgg	ttgtcttgc	aggttcccag aagaggaaga	agggggctgt	120
gaatttgc				126

<210> SEQ ID NO 256				
<211> LENGTH: 336				
<212> TYPE: DNA				
<213> ORGANISM: Artificial Sequence				
<220> FEATURE:				
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide				
<400> SEQUENCE: 256				
cgggttaaat ttcaagatc	cgcagacgt ccagcatacc	aacaggacaa aaaccaactc	60	
tataacgagc tgaatcttgg	aagaaggagg	aatatgtat tgctggataa	acggcgccgt	120
agagatccgg agatgggcgg	aaaaccaagg	cgaaaaacc ctcaggagg	actctacaac	180
gaactgcaga aagacaaaat	ggcggaggct	tattccgaaa taggcatgaa	gggcgagcgg	240
aggcgaggga aagggcacga	cggactgtat	caaggcctct	caaccgogac taaggatacg	300
tacgacgccc tgcacatgca	ggccctgcct	ccgaga		336

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<210> SEQ ID NO 257
<211> LENGTH: 493
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 257
```

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu  
1 5 10 15

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

Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe  
35 40 45

Thr	Phe	Ser	Ser	Tyr	Gly	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys
	50					55					60				

Gly Leu Glu Trp Val Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr  
 65                    70                    75                    80

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser  
85 90 95

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr  
           100                 105                 110

Ala Val Tyr Tyr Cys Gly Gly Ser Gly Tyr Ala Leu His Asp Asp Tyr  
115 120 125

Tyr Gly Leu Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser  
 130 135 140

Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln

Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser

Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn

Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met

Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe Ser

Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln

Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser Ser

Thr Leu Tyr Val Phe Gly Ser Gly Thr Lys Val Thr Val Leu Thr Thr

Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln

Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala

Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala

Pro-Lys-Ala-Gly-Thr-Cys-Gly-Val-Lys-Lys-Lys-Ser-Lys-Val-Ile-Thr

325                    330                    335

340                    345                    350

355                    360                    365

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

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

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

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

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

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

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

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

<210> SEQ ID NO 258  
 <211> LENGTH: 1479  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 258

atggccctcc	ctgtcaccgc	tctgttgctg	cccgcttgc	tcgtgtcca	cgcagcgcga	60
ccgcaggta	aattgcagga	gtctggaggc	ggtgtggtgc	aacccggtcg	cagttgcgc	120
ctgagttgt	ctgcgtctgg	atttacattt	tcatcttacg	aatgcatttgc	ggtaacgc	180
gcaccgggaa	aaggccttga	atgggtggct	gtatatttcat	acgatggttc	caacaatac	240
tatgctgact	cagtcaaggg	tcgatttaca	attagtcggg	acaactccaa	gaacaccctt	300
tatcttcaa	tgaattccct	tagagcagag	gatacggcgg	tctattactg	ttggggcagt	360
ggtttatgcac	ttcatgatga	ttactatggc	ttggatgtct	ggggcaagg	gacgttgtta	420
actgtatcct	ctgggtggtgg	ttggtagtgg	gggggaggct	ccggcggtgg	cggtctcaa	480
tctgctcta	ctcaaccaggc	aagegtatca	gggtcacccgg	gacagagtat	taccataagt	540
tgcacgggaa	cctctagcga	tgtagggggg	tataattatg	tatcttggta	tcaacaacac	600
ccggggaaag	cccctaaatt	gatgtatc	gacgtgagca	atcgacctag	tggcgatata	660
aatcgcttct	ctggtagcaa	gagtggaaat	acggcgccc	ttactattag	cggattgcaa	720
gcagaagatg	aggccgatta	ctactgcago	tcctatacta	gctcttctac	attgtacgtc	780
tttgggagcg	gacaaaagt	aacagtactc	acaacaacac	ctgccccgag	accgcctaca	840
ccagccccga	ctattgccag	ccagcctctg	agcctcaggc	ctgaggccctg	taggcccga	900
cgccggccgc	cagttcatac	acggggcttg	gatttcgttt	gtgatattta	tatttggct	960
cctttggccg	ggacatgtgg	cgtgtgtctt	ctgtcacttg	ttattacact	gtactgtaaa	1020
cgccggccgaa	aaaaatttgt	gtatatttt	aagcagccat	ttatgaggcc	cggtcagacg	1080
acgcaggagg	aggacggttg	ctcttgcagg	ttcccaagaag	aggaagaagg	gggtgtgaa	1140
ttgcgggtta	aatttcaag	atccgcagac	gctccagcat	accaacaggg	acaaaaccaa	1200
ctctataacg	agctgaatct	tggaaagaagg	gaggaatatg	atgtgttgc	taaacggcgc	1260
ggtagagatc	cgagatggg	cgaaaaacca	aggcgaaaaaa	accctcagga	gggactctac	1320

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aacgaactgc agaaagacaa aatggcggag gcttattccg aaataggcat gaagggcag	1380
cggagggag ggaaagggca cgacggactg tatcaaggcc tctcaaccgc gactaaggat	1440
acgtacgacg ccctgcacat gcaggccctg cctccgaga	1479

<210> SEQ ID NO 259  
<211> LENGTH: 1416  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 259

caggtacaat tgcaggagtc tggaggcggt gtggtgcaac ccggtegcag cttgcgcctg	60
agtttgtctg cgtctggatt tacatccc tcttacggaa tgcattgggt acgccaggca	120
ccggggaaag gccttgaatg ggtggctgta atttcatacg atggttccaa caaatactat	180
gctgactcg tcaagggtcg atttacaatt agtcgggaca actccaagaa caccctttat	240
cttcaaataatga attcccttag agcagaggat acggcggtct attactgtgg tggcagtgg	300
tatgcacttc atgatgatta ctatggcttg gatgtctggg ggcaaggggac gcttgtaact	360
gtatcctctg gtgggtgtgg tagtgggtggg ggaggctccg ggggtggcgg ctctcaatct	420
gctctgactc aaccagcaag cgtatcaggg tcaccgggac agagtattac cataagtgc	480
acggggacct ctagcgatgt aggggggtat aattatgtat ctggtatca acaacacccc	540
ggaaaagccc ctaaattgtat gatctacgac gtgagcaatc gacctagtgg cgtatcaaat	600
cgcttctctg gtagcaagag tggaaatacg gcgtccctta ctattagcg attgeaagca	660
gaagatgagg ccgattacta ctgcagctcc tatactagct ctctcacatt gtacgtctt	720
gggagcggaa caaaaagtaac agtactcaca acaacacctg ccccgagacc gcctacacca	780
cccccgacta ttgccagcca gcctctgago ctcaggcctg aggccctgttag gcccgcagcg	840
ggccgcgcag ttcatcacaacg gggcttggat ttgcattgtg atatttatat ttgggctct	900
ttggcgccgg catgtggcgt gctgtttctg tcacttggta ttacactgta ctgtaaacgc	960
gggcgaaaaa aattgtgtta tatttttaag cagccattta tgaggeccgt tcagacgacg	1020
caggaggagg acggttgctc ttgcagggttc ccagaagagg aagaaggggg ctgtgaattt	1080
cgggttaaat ttcaagatc cgcagacgtt ccagcatacc aacaggggaca aaaccaactc	1140
tataacgacg tgaatcttgg aagaaggagg gaatatgtat tgctggataa acggcgccgt	1200
agagatccgg agatgggcgg aaaaccaagg cgaaaaacc ctcaggagg actctacaac	1260
gaactgcaga aagacaaaat ggccggaggct tattccgaaa taggcattgaa gggcgagcgg	1320
aggcgaggga aagggcacga cggactgtat caaggcctct caaccgcac taaggatacg	1380
tacgacgccc tgcacatgca ggccctgcct ccgaga	1416

<210> SEQ ID NO 260  
<211> LENGTH: 369  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 260

caggtacaat tgcaggagtc tggaggcggt gtggtgcaac ccggtegcag cttgcgcctg	60
agtttgtctg cgtctggatt tacatccc tcttacggaa tgcattgggt acgccaggca	120

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ccggggaaag gccttgaatg ggtggctgta atttcatacg atggttccaa caaatactat	180
gctgactcg tcaagggtcg atttacaatt agtccccaca actccaagaa caccctttat	240
cttcaaatga attcccttag agcagaggat acggcggtct attactgtgg tggcagtgg	300
tatgcacttc atgatgatta ctatggcttg gatgtctggg ggcaaggac gcttgtaact	360
gtatccctct	369

<210> SEQ ID NO 261  
<211> LENGTH: 333  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 261

caatctgctc tgactcaacc agcaagcgta tcagggtcac cgggacagag tattaccata	60
agttgcacgg ggacctctag cgatgttaggg gggataatt atgtatctg gtatcaacaa	120
caccccccggaa aagccccctaa attgtatgtc tacgacgtga gcaatcgacc tagtggcgta	180
tcaaatacgct tctctggtag caagagtggg aatacggcgt cccttactat tagcggattg	240
caaggcagaag atgaggccga ttactactgc agtcctata cttagctctc tacattgtac	300
gtctttggga gcgaaacaaa agtaacagta ctc	333

<210> SEQ ID NO 262  
<211> LENGTH: 345  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 262

gaagtgaat tgggtggaaatc agggggagga cttgtgcagc ctggaggatc gctgagactg	60
tcatgtgccg tgtccggctt tgccctgtcc aaccacggga tggctctgggt ccgcgcgcgc	120
cctggaaagg gctcgaatg ggtgtcggtt attgtgtaca gggtagcac ctactatgcc	180
gcatccgtga aggggagatt caccatcago cgggacaact ccaggaacac tctgtacctc	240
caaataatgcattt cgctgaggcc agaggacact gccatctact actgctccgc gcatggcgga	300
gagtccgacg tctggggaca ggggaccacc gtgaccgtgt cttagc	345

<210> SEQ ID NO 263  
<211> LENGTH: 321  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 263

gacatccagc tcacccagtc cccgagctcg ctgtccgcct ccgtgggaga tcgggtcacc	60
atcacgtgcc ggcgcagcca gtcgatttcc tcctacctga actggtagca acagaagccc	120
ggaaaaagccc cgaagcttct catctacgac gcctcgagcc tgcagtcagg agtgcctca	180
cggttctccg gtcgggttc cggtactgtat ttacccctga ccatttccctc cctgcacac	240
gaggacttcg ctacttacta ctgcacagcag tgcgtactcca cccctacac ttccggacaa	300
ggcaccaagg tcgaaatcaa g	321

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&lt;210&gt; SEQ ID NO 264

&lt;400&gt; SEQUENCE: 264

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&lt;210&gt; SEQ ID NO 265

&lt;400&gt; SEQUENCE: 265

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&lt;210&gt; SEQ ID NO 266

&lt;400&gt; SEQUENCE: 266

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&lt;210&gt; SEQ ID NO 273

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&lt;210&gt; SEQ ID NO 274

&lt;400&gt; SEQUENCE: 274

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<210> SEQ ID NO 275  
<211> LENGTH: 132  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 275

Asp	Val	Pro	Asp	Tyr	Ala	Ser	Leu	Gly	Gly	Pro	Ser	Ser	Pro	Lys	Lys
1								5		10				15	

Lys	Arg	Lys	Val	Ser	Arg	Gly	Val	Gln	Val	Glu	Thr	Ile	Ser	Pro	Gly
								20		25				30	

Asp	Gly	Arg	Thr	Phe	Pro	Lys	Arg	Gly	Gln	Thr	Cys	Val	Val	His	Tyr
								35		40			45		

Thr	Gly	Met	Leu	Glu	Asp	Gly	Lys	Lys	Phe	Asp	Ser	Ser	Arg	Asp	Arg
								50		55			60		

Asn	Lys	Pro	Phe	Lys	Phe	Met	Leu	Gly	Lys	Gln	Glu	Val	Ile	Arg	Gly
								65		70			80		

Trp	Glu	Gly	Val	Ala	Gln	Met	Ser	Val	Gly	Gln	Arg	Ala	Lys	Leu
								85		90			95	

Thr	Ile	Ser	Pro	Asp	Tyr	Ala	Tyr	Gly	Ala	Thr	Gly	His	Pro	Gly	Ile
								100		105			110		

Ile	Pro	Pro	His	Ala	Thr	Leu	Val	Phe	Asp	Val	Glu	Leu	Leu	Lys	Leu
								115		120			125		

Glu	Thr	Ser	Tyr												
								130							

<210> SEQ ID NO 276  
<211> LENGTH: 108  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 276

Val	Gln	Val	Glu	Thr	Ile	Ser	Pro	Gly	Asp	Gly	Arg	Thr	Phe	Pro	Lys
1								5		10			15		

Arg	Gly	Gln	Thr	Cys	Val	Val	His	Tyr	Thr	Gly	Met	Leu	Glu	Asp	Gly
								20		25			30		

Lys	Lys	Phe	Asp	Ser	Ser	Arg	Asp	Arg	Asn	Lys	Pro	Phe	Lys	Phe	Met
								35		40			45		

Leu	Gly	Lys	Gln	Glu	Val	Ile	Arg	Gly	Trp	Glu	Glu	Gly	Val	Ala	Gln
								50		55			60		

Met	Ser	Val	Gly	Gln	Arg	Ala	Lys	Leu	Thr	Ile	Ser	Pro	Asp	Tyr	Ala
								65		70			80		

Tyr	Gly	Ala	Thr	Gly	His	Pro	Gly	Ile	Ile	Pro	Pro	His	Ala	Thr	Leu
								85		90			95		

Val	Phe	Asp	Val	Glu	Leu	Leu	Lys	Leu	Glu	Thr	Ser				
								100		105					

<210> SEQ ID NO 277  
<211> LENGTH: 93  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 277

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Ile Leu Trp His Glu Met Trp His Glu Gly Leu Glu Ala Ser Arg  
 1               5               10               15  
 Leu Tyr Phe Gly Glu Arg Asn Val Lys Gly Met Phe Glu Val Leu Glu  
 20               25               30  
 Pro Leu His Ala Met Met Glu Arg Gly Pro Gln Thr Leu Lys Glu Thr  
 35               40               45  
 Ser Phe Asn Gln Ala Tyr Gly Arg Asp Leu Met Glu Ala Gln Glu Trp  
 50               55               60  
 Cys Arg Lys Tyr Met Lys Ser Gly Asn Val Lys Asp Leu Thr Gln Ala  
 65               70               75               80  
 Trp Asp Leu Tyr Tyr His Val Phe Arg Arg Ile Ser Lys  
 85               90

<210> SEQ ID NO 278  
<211> LENGTH: 95  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 278

Ile Leu Trp His Glu Met Trp His Glu Gly Leu Ile Glu Ala Ser Arg  
 1               5               10               15  
 Leu Tyr Phe Gly Glu Arg Asn Val Lys Gly Met Phe Glu Val Leu Glu  
 20               25               30  
 Pro Leu His Ala Met Met Glu Arg Gly Pro Gln Thr Leu Lys Glu Thr  
 35               40               45  
 Ser Phe Asn Gln Ala Tyr Gly Arg Asp Leu Met Glu Ala Gln Glu Trp  
 50               55               60  
 Cys Arg Lys Tyr Met Lys Ser Gly Asn Val Lys Asp Leu Thr Gln Ala  
 65               70               75               80  
 Trp Asp Leu Tyr Tyr His Val Phe Arg Arg Ile Ser Lys Thr Ser  
 85               90               95

<210> SEQ ID NO 279  
<211> LENGTH: 95  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 279

Ile Leu Trp His Glu Met Trp His Glu Gly Leu Leu Glu Ala Ser Arg  
 1               5               10               15  
 Leu Tyr Phe Gly Glu Arg Asn Val Lys Gly Met Phe Glu Val Leu Glu  
 20               25               30  
 Pro Leu His Ala Met Met Glu Arg Gly Pro Gln Thr Leu Lys Glu Thr  
 35               40               45  
 Ser Phe Asn Gln Ala Tyr Gly Arg Asp Leu Met Glu Ala Gln Glu Trp  
 50               55               60  
 Cys Arg Lys Tyr Met Lys Ser Gly Asn Val Lys Asp Leu Thr Gln Ala  
 65               70               75               80  
 Trp Asp Leu Tyr Tyr His Val Phe Arg Arg Ile Ser Lys Thr Ser  
 85               90               95

&lt;210&gt; SEQ ID NO 280



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20                    25                    30

Pro Leu His Ala Met Met Glu Arg Gly Pro Gln Thr Leu Lys Glu Thr  
 35                    40                    45

Ser Phe Asn Gln Ala Tyr Gly Arg Asp Leu Met Glu Ala Gln Glu Trp  
 50                    55                    60

Cys Arg Lys Tyr Met Lys Ser Gly Asn Val Lys Asp Leu Leu Gln Ala  
 65                    70                    75                    80

Trp Asp Leu Tyr Tyr His Val Phe Arg Arg Ile Ser Lys Thr Ser  
 85                    90                    95

&lt;210&gt; SEQ ID NO 283

&lt;211&gt; LENGTH: 95

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 283

Ile Leu Trp His Glu Met Trp His Glu Gly Leu Leu Glu Ala Ser Arg  
 1                    5                    10                    15

Leu Tyr Phe Gly Glu Arg Asn Val Lys Gly Met Phe Glu Val Leu Glu  
 20                    25                    30

Pro Leu His Ala Met Met Glu Arg Gly Pro Gln Thr Leu Lys Glu Thr  
 35                    40                    45

Ser Phe Asn Gln Ala Tyr Gly Arg Asp Leu Met Glu Ala Gln Glu Trp  
 50                    55                    60

Cys Arg Lys Tyr Met Lys Ser Gly Asn Val Lys Asp Leu Leu Gln Ala  
 65                    70                    75                    80

Trp Asp Leu Tyr Tyr His Val Phe Arg Arg Ile Ser Lys Thr Ser  
 85                    90                    95

&lt;210&gt; SEQ ID NO 284

&lt;211&gt; LENGTH: 1132

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Homo sapiens

&lt;400&gt; SEQUENCE: 284

Met Pro Arg Ala Pro Arg Cys Arg Ala Val Arg Ser Leu Leu Arg Ser  
 1                    5                    10                    15

His Tyr Arg Glu Val Leu Pro Leu Ala Thr Phe Val Arg Arg Leu Gly  
 20                    25                    30

Pro Gln Gly Trp Arg Leu Val Gln Arg Gly Asp Pro Ala Ala Phe Arg  
 35                    40                    45

Ala Leu Val Ala Gln Cys Leu Val Cys Val Pro Trp Asp Ala Arg Pro  
 50                    55                    60

Pro Pro Ala Ala Pro Ser Phe Arg Gln Val Ser Cys Leu Lys Glu Leu  
 65                    70                    75                    80

Val Ala Arg Val Leu Gln Arg Leu Cys Glu Arg Gly Ala Lys Asn Val  
 85                    90                    95

Leu Ala Phe Gly Phe Ala Leu Leu Asp Gly Ala Arg Gly Pro Pro  
 100                    105                    110

Glu Ala Phe Thr Thr Ser Val Arg Ser Tyr Leu Pro Asn Thr Val Thr  
 115                    120                    125

Asp Ala Leu Arg Gly Ser Gly Ala Trp Gly Leu Leu Leu Arg Arg Val  
 130                    135                    140

Gly Asp Asp Val Leu Val His Leu Leu Ala Arg Cys Ala Leu Phe Val

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145	150	155	160
Leu Val Ala Pro Ser Cys Ala Tyr Gln Val Cys Gly Pro Pro Leu Tyr			
165	170	175	
Gln Leu Gly Ala Ala Thr Gln Ala Arg Pro Pro Pro His Ala Ser Gly			
180	185	190	
Pro Arg Arg Arg Leu Gly Cys Glu Arg Ala Trp Asn His Ser Val Arg			
195	200	205	
Glu Ala Gly Val Pro Leu Gly Leu Pro Ala Pro Gly Ala Arg Arg Arg			
210	215	220	
Gly Gly Ser Ala Ser Arg Ser Leu Pro Leu Pro Lys Arg Pro Arg Arg			
225	230	235	240
Gly Ala Ala Pro Glu Pro Glu Arg Thr Pro Val Gly Gln Gly Ser Trp			
245	250	255	
Ala His Pro Gly Arg Thr Arg Gly Pro Ser Asp Arg Gly Phe Cys Val			
260	265	270	
Val Ser Pro Ala Arg Pro Ala Glu Glu Ala Thr Ser Leu Glu Gly Ala			
275	280	285	
Leu Ser Gly Thr Arg His Ser His Pro Ser Val Gly Arg Gln His His			
290	295	300	
Ala Gly Pro Pro Ser Thr Ser Arg Pro Pro Arg Pro Trp Asp Thr Pro			
305	310	315	320
Cys Pro Pro Val Tyr Ala Glu Thr Lys His Phe Leu Tyr Ser Ser Gly			
325	330	335	
Asp Lys Glu Gln Leu Arg Pro Ser Phe Leu Leu Ser Ser Leu Arg Pro			
340	345	350	
Ser Leu Thr Gly Ala Arg Arg Leu Val Glu Thr Ile Phe Leu Gly Ser			
355	360	365	
Arg Pro Trp Met Pro Gly Thr Pro Arg Arg Leu Pro Arg Leu Pro Gln			
370	375	380	
Arg Tyr Trp Gln Met Arg Pro Leu Phe Leu Glu Leu Leu Gly Asn His			
385	390	395	400
Ala Gln Cys Pro Tyr Gly Val Leu Leu Lys Thr His Cys Pro Leu Arg			
405	410	415	
Ala Ala Val Thr Pro Ala Ala Gly Val Cys Ala Arg Glu Lys Pro Gln			
420	425	430	
Gly Ser Val Ala Ala Pro Glu Glu Asp Thr Asp Pro Arg Arg Leu			
435	440	445	
Val Gln Leu Leu Arg Gln His Ser Ser Pro Trp Gln Val Tyr Gly Phe			
450	455	460	
Val Arg Ala Cys Leu Arg Arg Leu Val Pro Pro Gly Leu Trp Gly Ser			
465	470	475	480
Arg His Asn Glu Arg Arg Phe Leu Arg Asn Thr Lys Lys Phe Ile Ser			
485	490	495	
Leu Gly Lys His Ala Lys Leu Ser Leu Gln Glu Leu Thr Trp Lys Met			
500	505	510	
Ser Val Arg Gly Cys Ala Trp Leu Arg Arg Ser Pro Gly Val Gly Cys			
515	520	525	
Val Pro Ala Ala Glu His Arg Leu Arg Glu Glu Ile Leu Ala Lys Phe			
530	535	540	
Leu His Trp Leu Met Ser Val Tyr Val Val Glu Leu Leu Arg Ser Phe			
545	550	555	560
Phe Tyr Val Thr Glu Thr Phe Gln Lys Asn Arg Leu Phe Phe Tyr			
565	570	575	

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Arg Lys Ser Val Trp Ser Lys Leu Gln Ser Ile Gly Ile Arg Gln His  
 580 585 590  
 Leu Lys Arg Val Gln Leu Arg Glu Leu Ser Glu Ala Glu Val Arg Gln  
 595 600 605  
 His Arg Glu Ala Arg Pro Ala Leu Leu Thr Ser Arg Leu Arg Phe Ile  
 610 615 620  
 Pro Lys Pro Asp Gly Leu Arg Pro Ile Val Asn Met Asp Tyr Val Val  
 625 630 635 640  
 Gly Ala Arg Thr Phe Arg Arg Glu Lys Arg Ala Glu Arg Leu Thr Ser  
 645 650 655  
 Arg Val Lys Ala Leu Phe Ser Val Leu Asn Tyr Glu Arg Ala Arg Arg  
 660 665 670  
 Pro Gly Leu Leu Gly Ala Ser Val Leu Gly Leu Asp Asp Ile His Arg  
 675 680 685  
 Ala Trp Arg Thr Phe Val Leu Arg Val Arg Ala Gln Asp Pro Pro Pro  
 690 695 700  
 Glu Leu Tyr Phe Val Lys Val Asp Val Thr Gly Ala Tyr Asp Thr Ile  
 705 710 715 720  
 Pro Gln Asp Arg Leu Thr Glu Val Ile Ala Ser Ile Ile Lys Pro Gln  
 725 730 735  
 Asn Thr Tyr Cys Val Arg Arg Tyr Ala Val Val Gln Lys Ala Ala His  
 740 745 750  
 Gly His Val Arg Lys Ala Phe Lys Ser His Val Ser Thr Leu Thr Asp  
 755 760 765  
 Leu Gln Pro Tyr Met Arg Gln Phe Val Ala His Leu Gln Glu Thr Ser  
 770 775 780  
 Pro Leu Arg Asp Ala Val Val Ile Glu Gln Ser Ser Ser Leu Asn Glu  
 785 790 795 800  
 Ala Ser Ser Gly Leu Phe Asp Val Phe Leu Arg Phe Met Cys His His  
 805 810 815  
 Ala Val Arg Ile Arg Gly Lys Ser Tyr Val Gln Cys Gln Gly Ile Pro  
 820 825 830  
 Gln Gly Ser Ile Leu Ser Thr Leu Leu Cys Ser Leu Cys Tyr Gly Asp  
 835 840 845  
 Met Glu Asn Lys Leu Phe Ala Gly Ile Arg Arg Asp Gly Leu Leu Leu  
 850 855 860  
 Arg Leu Val Asp Asp Phe Leu Leu Val Thr Pro His Leu Thr His Ala  
 865 870 875 880  
 Lys Thr Phe Leu Arg Thr Leu Val Arg Gly Val Pro Glu Tyr Gly Cys  
 885 890 895  
 Val Val Asn Leu Arg Lys Thr Val Val Asn Phe Pro Val Glu Asp Glu  
 900 905 910  
 Ala Leu Gly Gly Thr Ala Phe Val Gln Met Pro Ala His Gly Leu Phe  
 915 920 925  
 Pro Trp Cys Gly Leu Leu Asp Thr Arg Thr Leu Glu Val Gln Ser  
 930 935 940  
 Asp Tyr Ser Ser Tyr Ala Arg Thr Ser Ile Arg Ala Ser Leu Thr Phe  
 945 950 955 960  
 Asn Arg Gly Phe Lys Ala Gly Arg Asn Met Arg Arg Lys Leu Phe Gly  
 965 970 975  
 Val Leu Arg Leu Lys Cys His Ser Leu Phe Leu Asp Leu Gln Val Asn  
 980 985 990

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Ser Leu Gln Thr Val Cys Thr Asn Ile Tyr Lys Ile Leu Leu Leu Gln  
 995 1000 1005

Ala Tyr Arg Phe His Ala Cys Val Leu Gln Leu Pro Phe His Gln  
 1010 1015 1020

Gln Val Trp Lys Asn Pro Thr Phe Phe Leu Arg Val Ile Ser Asp  
 1025 1030 1035

Thr Ala Ser Leu Cys Tyr Ser Ile Leu Lys Ala Lys Asn Ala Gly  
 1040 1045 1050

Met Ser Leu Gly Ala Lys Gly Ala Ala Gly Pro Leu Pro Ser Glu  
 1055 1060 1065

Ala Val Gln Trp Leu Cys His Gln Ala Phe Leu Leu Lys Leu Thr  
 1070 1075 1080

Arg His Arg Val Thr Tyr Val Pro Leu Leu Gly Ser Leu Arg Thr  
 1085 1090 1095

Ala Gln Thr Gln Leu Ser Arg Lys Leu Pro Gly Thr Thr Leu Thr  
 1100 1105 1110

Ala Leu Glu Ala Ala Ala Asn Pro Ala Leu Pro Ser Asp Phe Lys  
 1115 1120 1125

Thr Ile Leu Asp  
 1130

<210> SEQ ID NO 285  
 <211> LENGTH: 253  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 285

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

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Met Leu Ser Asn  
 20 25 30

Ser Asp Thr Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu  
 35 40 45

Trp Leu Gly Arg Thr Tyr His Arg Ser Thr Trp Tyr Asp Asp Tyr Ala  
 50 55 60

Ser Ser Val Arg Gly Arg Val Ser Ile Asn Val Asp Thr Ser Lys Asn  
 65 70 75 80

Gln Tyr Ser Leu Gln Leu Asn Ala Val Thr Pro Glu Asp Thr Gly Val  
 85 90 95

Tyr Tyr Cys Ala Arg Val Arg Leu Gln Asp Gly Asn Ser Trp Ser Asp  
 100 105 110

Ala Phe Asp Val Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly  
 115 120 125

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

Ala Leu Thr Gln Pro Ala Ser Ala Ser Gly Ser Pro Gly Gln Ser Val  
 145 150 155 160

Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr  
 165 170 175

Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile  
 180 185 190

Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly  
 195 200 205

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Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala  
 210                    215                    220

Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser Ser Thr  
 225                    230                    235                    240

Leu Tyr Val Phe Gly Thr Gly Thr Gln Leu Thr Val Leu  
 245                    250

&lt;210&gt; SEQ ID NO 286

&lt;211&gt; LENGTH: 127

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 286

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

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Met Leu Ser Asn  
 20                    25                    30

Ser Asp Thr Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu  
 35                    40                    45

Trp Leu Gly Arg Thr Tyr His Arg Ser Thr Trp Tyr Asp Asp Tyr Ala  
 50                    55                    60

Ser Ser Val Arg Gly Arg Val Ser Ile Asn Val Asp Thr Ser Lys Asn  
 65                    70                    75                    80

Gln Tyr Ser Leu Gln Leu Asn Ala Val Thr Pro Glu Asp Thr Gly Val  
 85                    90                    95

Tyr Tyr Cys Ala Arg Val Arg Leu Gln Asp Gly Asn Ser Trp Ser Asp  
 100                    105                    110

Ala Phe Asp Val Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser  
 115                    120                    125

&lt;210&gt; SEQ ID NO 287

&lt;211&gt; LENGTH: 111

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 287

Gln Ser Ala Leu Thr Gln Pro Ala Ser Ala Ser Gly Ser Pro Gly Gln  
 1                    5                    10                    15

Ser Val Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr  
 20                    25                    30

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

Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe  
 50                    55                    60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu  
 65                    70                    75                    80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser  
 85                    90                    95

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

&lt;210&gt; SEQ ID NO 288

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<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      peptide
```

<400> SEQUENCE: 288

Gly Asp Ser Met Leu Ser Asn Ser Asp Thr Trp Asn  
 1 5 10

<210> SEQ ID NO 289

```
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description
                  peptide
```

<400> SEQUENCE: 289

Ser Asn Ser Asp Thr Trp Asn  
1 5

<210> SEQ ID NO 290

```
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description
      peptide
```

<400> SEQUENCE: 290

Arg Thr Tyr His Arg Ser Thr Trp Tyr Asp Asp Tyr Ala Ser Ser Val  
 1 5 10 15

Arg Gly

<210> SEQ ID NO 291

```
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description
      peptide
```

<400> SEQUENCE: 291

Val	Arg	Leu	Gln	Asp	Gly	Asn	Ser	Trp	Ser	Asp	Ala	Phe	Asp	Val
1				5					10					15

<210> SEQ ID NO 292

```
<211> LENGTH: 465
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description
      polypeptide
```

<400> SEQUENCE: 292

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

Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr  
20 25 30

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

Tyr His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly  
50 55 60

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Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln  
 65 70 75 80

Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr  
 85 90 95

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

Gly Gly Gly Ser Gly Gly Ser Glu Val Lys Leu Gln Glu  
 115 120 125

Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys  
 130 135 140

Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg  
 145 150 155 160

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

Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile  
 180 185 190

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

Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly  
 210 215 220

Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val  
 225 230 235 240

Ser Ser Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr  
 245 250 255

Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala  
 260 265 270

Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile  
 275 280 285

Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser  
 290 295 300

Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr  
 305 310 315 320

Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu  
 325 330 335

Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Gly Cys Glu  
 340 345 350

Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln  
 355 360 365

Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu  
 370 375 380

Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly  
 385 390 395 400

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

Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu  
 420 425 430

Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr  
 435 440 445

Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro  
 450 455 460

Arg  
465



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Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro  
 65 70 75 80  
 Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr  
 85 90 95  
 Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Ser  
 100 105 110  
 Gly Gly Gly Ser Gly Gly Gly Ser Gln Val Gln Leu Gln Glu  
 115 120 125  
 Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys  
 130 135 140  
 Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg  
 145 150 155 160  
 Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly Val Ile Trp Gly Ser  
 165 170 175  
 Glu Thr Thr Tyr Tyr Gln Ser Ser Leu Lys Ser Arg Val Thr Ile Ser  
 180 185 190  
 Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr  
 195 200 205  
 Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly  
 210 215 220  
 Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val  
 225 230 235 240  
 Ser Ser Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr  
 245 250 255  
 Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala  
 260 265 270  
 Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile  
 275 280 285  
 Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser  
 290 295 300  
 Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr  
 305 310 315 320  
 Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu  
 325 330 335  
 Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Gly Cys Glu  
 340 345 350  
 Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln  
 355 360 365  
 Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu  
 370 375 380  
 Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly  
 385 390 395 400  
 Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln  
 405 410 415  
 Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu  
 420 425 430  
 Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr  
 435 440 445  
 Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro  
 450 455 460  
 Arg  
 465

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<210> SEQ ID NO 295  
<211> LENGTH: 5  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 295

Asp	Tyr	Gly	Val	Ser
1				5

<210> SEQ ID NO 296  
<211> LENGTH: 16  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 296

Val	Ile	Trp	Gly	Ser	Glu	Thr	Thr	Tyr	Tyr	Asn	Ser	Ala	Leu	Lys	Ser
1					5			10					15		

<210> SEQ ID NO 297  
<211> LENGTH: 12  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 297

His	Tyr	Tyr	Tyr	Gly	Gly	Ser	Tyr	Ala	Met	Asp	Tyr
1					5			10			

<210> SEQ ID NO 298  
<211> LENGTH: 11  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 298

Arg	Ala	Ser	Gln	Asp	Ile	Ser	Lys	Tyr	Leu	Asn
1					5			10		

<210> SEQ ID NO 299  
<211> LENGTH: 7  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 299

His	Thr	Ser	Arg	Leu	His	Ser
1					5	

<210> SEQ ID NO 300  
<211> LENGTH: 9  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

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&lt;400&gt; SEQUENCE: 300

Gln Gln Gly Asn Thr Leu Pro Tyr Thr  
1 5

<210> SEQ ID NO 301  
<211> LENGTH: 486  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 301

Met Ala Leu Pro Val Thr Ala Leu Leu Pro Leu Ala Leu Leu Leu  
1 5 10 15His Ala Ala Arg Pro Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu  
20 25 30Ser Ala Ser Leu Gly Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln  
35 40 45Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr  
50 55 60Val Lys Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Val Pro  
65 70 75 80Ser Arg Phe Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile  
85 90 95Ser Asn Leu Glu Gln Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly  
100 105 110Asn Thr Leu Pro Tyr Thr Phe Gly Gly Thr Lys Leu Glu Ile Thr  
115 120 125Gly Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Ser Gly  
130 135 140Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser  
145 150 155 160Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly  
165 170 175Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly  
180 185 190Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser  
195 200 205Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys  
210 215 220Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys  
225 230 235 240His Tyr Tyr Tyr Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly  
245 250 255Thr Ser Val Thr Val Ser Ser Thr Thr Pro Ala Pro Arg Pro Pro  
260 265 270Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu  
275 280 285Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp  
290 295 300Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly  
305 310 315 320Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg  
325 330 335

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

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

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

Pro Ala Tyr Lys Gln Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu  
385 390 395 400

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

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu  
420 425 430

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

Gly Met Lys Gly Glu Arg Arg Gly Lys Gly His Asp Gly Leu Tyr  
450 455 460

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

Gln Ala Leu Pro Pro Arg  
485

<210> SEQ ID NO 302  
<211> LENGTH: 1458  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 302

```

atggccttac cagtgaccgc cttgtcctg ccgtgtggct tgcgtgtcca cgccgccagg   60
ccggacatcc agatgacaca gactacatcc tccctgtctg cctctctggg agacagagtc  120
accatcaattt gcagggcaag tcaggacatt agtaaatatt taaatttgta tcagcagaaa  180
ccagatggaa ctgttaaact cctgtatctac catacatcaa gattacactc aggagtccca  240
tcaagggttca gtggcagtgg gtctggaaaca gattattctc tcaccattag caacctggag 300
caagaagata ttgccactta cttttgccaa caggtaata cgcttcgtt cacgttccga 360
ggggggacca agctggagat cacaggtggc ggtggctgg gggtgggtgg gtcgggtggc 420
ggcgatctg aggtgaaact gcaggagtca ggacctggc tggtggcgcc ctcacagagc 480
ctgtccgtca catgcactgt ctcagggttc tcattacccg actatggtgt aagctggatt 540
cgccagcctc cacgaaaggg tctggagtgg ctggagtaa tatgggttag tgaaaccaca 600
tactataattt cagctctcaa atccagactg accatcatca aggacaactc caagagccaa 660
gttttcttaa aaatgaacag tctgcaaact gatgacacag ccatttacta ctgtgccaaa 720
cattattact acgggtggtag ctatgctatg gactactggg gccaaggAAC ctcagtccacc 780
gtctccctcaa ccacgacgccc agcgccgcga ccaccaacac cggccgcacac catcgctcg 840
cagccccctgt ccctgtggcc agaggcgtgc cggccagcggc cggggggcgcc agtgcacacg 900
agggggctgg acttcgcctg tgatatatctac atctgggcgc cttggccgg gacttgggg 960
gtccttctcc tgtcaactggt tatcacccct tactgcaaac gggcagaaaa gaaactcctg 1020
tatatatattca aacaaccatt tatgagacca gtacaaacta ctcaagagga agatggctgt 1080
agctgcccgtt ttccagaaga agaagaagga ggatgtgaac tgagagtgaa gttcagcagg 1140

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agcgcacgacg	cccccgcgta	caagcaggc	cagaaccaggc	tctataacga	gctcaatcta	1200
ggacgaagag	aggagtacga	tgtttggac	aagagacgtg	gccgggaccc	tgagatgggg	1260
ggaaagccga	gaaggaagaa	ccctcaggaa	ggcctgtaca	atgaactgca	gaaagataag	1320
atggcggagg	cctacagtga	gattgggatg	aaaggcgagc	gccggagggg	caagggcac	1380
gatggcctt	accagggtct	cagtacagcc	accaaggaca	cctacgacgc	ccttcacatg	1440
caggccctgc	cccctcgc					1458

<210> SEQ ID NO 303  
<211> LENGTH: 242  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 303

Asp	Ile	Gln	Met	Thr	Gln	Thr	Thr	Ser	Ser	Leu	Ser	Ala	Ser	Leu	Gly
1															15

Asp	Arg	Val	Thr	Ile	Ser	Cys	Arg	Ala	Ser	Gln	Asp	Ile	Ser	Lys	Tyr
20															30

Leu	Asn	Trp	Tyr	Gln	Gln	Lys	Pro	Asp	Gly	Thr	Val	Lys	Leu	Leu	Ile
35															

Tyr	His	Thr	Ser	Arg	Leu	His	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
50															

Ser	Gly	Ser	Gly	Thr	Asp	Tyr	Ser	Leu	Thr	Ile	Ser	Asn	Leu	Glu	Gln
65															

Glu	Asp	Ile	Ala	Thr	Tyr	Phe	Cys	Gln	Gln	Gly	Asn	Thr	Leu	Pro	Tyr
85															

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

Gly	Gly	Gly	Ser	Gly	Gly	Gly	Ser	Glu	Val	Lys	Leu	Gln	Glu		
115															

Ser	Gly	Pro	Gly	Leu	Val	Ala	Pro	Ser	Gln	Ser	Leu	Ser	Val	Thr	Cys
130															

Thr	Val	Ser	Gly	Val	Ser	Leu	Pro	Asp	Tyr	Gly	Val	Ser	Trp	Ile	Arg
145															

Gln	Pro	Pro	Arg	Lys	Gly	Leu	Glu	Trp	Leu	Gly	Val	Ile	Trp	Gly	Ser
165															

Glu	Thr	Thr	Tyr	Tyr	Asn	Ser	Ala	Leu	Lys	Ser	Arg	Leu	Thr	Ile	Ile
180															

Lys	Asp	Asn	Ser	Lys	Ser	Gln	Val	Phe	Leu	Lys	Met	Asn	Ser	Leu	Gln
195															

Thr	Asp	Asp	Thr	Ala	Ile	Tyr	Tyr	Cys	Ala	Lys	His	Tyr	Tyr	Tyr	Gly
210															

Gly	Ser	Tyr	Ala	Met	Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Ser	Val	Thr	Val
225															

Ser Ser

<210> SEQ ID NO 304  
<211> LENGTH: 16  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

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&lt;400&gt; SEQUENCE: 304

Val	Ile	Trp	Gly	Ser	Glu	Thr	Thr	Tyr	Tyr	Gln	Ser	Ser	Ser	Leu	Lys	Ser
1					5			10						15		

&lt;210&gt; SEQ ID NO 305

&lt;211&gt; LENGTH: 726

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 305

gaaattgtga	tgaccaggc	acccgcact	cttagcctt	cacccggta	gcgcgcaacc	60	
ctgtcttgc	a	gagctccca	agacatctca	aaatacctta	attggtatca	acagaaggcc	120
ggacaggc	tc	tcgccttct	gatctaccac	accagccggc	tccattctgg	aatccctgcc	180
aggttcagcg	gt	ageggate	tgggaccgac	tacaccctca	ctatcagctc	actgcagcca	240
gaggactcg	ctgtcttattt	ctgtcagcaa	gggaacaccc	tgcctacac	ctttggacag	300	
ggcaccaagc	tc	cgagattaa	aggtggaggt	ggcagcggag	gaggtgggtc	cggcgggtgga	360
ggaagccagg	tccaa	cttcaactcca	agaaaagcgg	ccgggtcttgc	tgaagccatc	agaaaactctt	420
tcactgactt	gtactgtgag	cggagtgtct	ctccccgatt	acgggggtgtc	ttggatcaga	480	
cagccacccg	g	gaagggtct	ggaatggatt	ggagtgattt	ggggctctga	gactacttac	540
taccaatcat	ccctcaagtc	acgcgtcacc	atctcaaagg	acaactctaa	gaatcaggtg	600	
tcactgaaac	tgtcatctgt	gaccgcagcc	gacaccgcgg	tgtactatttgc	cgctaagcat	660	
tactattatg	gcgggagcta	cgcaatggat	tactgggac	agggtactct	ggtcaccgtg	720	
tccagc						726	

&lt;210&gt; SEQ ID NO 306

&lt;211&gt; LENGTH: 486

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 306

Met	Ala	Leu	Pro	Val	Thr	Ala	Leu	Leu	Leu	Pro	Leu	Ala	Leu	Leu	Leu
1						5		10			15				

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

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

Asp	Ile	Ser	Lys	Tyr	Leu	Asn	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala
						50		55		60					

Pro	Arg	Leu	Leu	Ile	Tyr	His	Thr	Ser	Arg	Leu	His	Ser	Gly	Ile	Pro
65						70		75		80					

Ala	Arg	Phe	Ser	Gly	Ser	Gly	Thr	Asp	Tyr	Thr	Leu	Thr	Ile		
						85		90		95					

Ser	Ser	Leu	Gln	Pro	Glu	Asp	Phe	Ala	Val	Tyr	Phe	Cys	Gln	Gln	Gly
						100		105		110					

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

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

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

Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly  
165 170 175

Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly  
180 185 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Gln Ser Ser Leu Lys Ser  
195 200 205

Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys  
210 215 220

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

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly  
245 250 255

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

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

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

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

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

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

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

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

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu  
385 390 395 400

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

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu  
420 425 430

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

Gly Met Lys Gly Glu Arg Arg Gly Lys Gly His Asp Gly Leu Tyr  
450 455 460

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

Gln Ala Leu Pro Pro Arg  
485

<210> SEQ ID NO 307  
<211> LENGTH: 1458  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
polynucleotide

&lt;400&gt; SEQUENCE: 307

atggccctcc ctgtcaccgc cctgctgctt ccgcgtggctc ttctgctcca cgccgctcg 60

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cccgaaattg tgatgaccca gtcacccgcc actcttagcc tttcacccgg tgagcgcga      120
accctgttcc gcagagccctc ccaagacata taaaataacc ttaattggta tcaacagaag      180
ccccggacagg ctccctcgccct tctgatctac cacaccagcc ggetccatcc tggaatccct      240
gccaggttca gcggttagcgg atctgggacc gactacaccc tcactatcag ctcactgcag      300
ccagaggact tcgctgtcta tttctgtcag caagggaaaca ccctgcctta cacctttgga      360
cagggcacca agctcgagat taaaggtgga ggtggcagcg gaggagggtgg gtccggcggt      420
ggaggaagcc aggtccaact ccaagaaagg ggaccgggtc ttgtgaagcc atcagaaact      480
cttcactga ctgtactgt gageggagtg tctctccccc attacgggggt gtcttgatc      540
agacagccac cgggaaaggg tctggaatgg attggagtga tttggggctc tgagactact      600
tactaccaat catccctcaa gtcacgcgtc accatctcaa aggacaactc taagaatcag      660
gtgtcactga aactgtcatc tgtgaccgca gccgacaccc cggtgtacta ttgcgctaa      720
cattactatt atggcgggag ctacgcaatg gattactggg gacagggtac tctggtcacc      780
gtgtccagca ccactacccc agcacccgagg ccacccaccc cggctctac catgcctcc      840
cagcctctgt ccctgcgtcc ggaggcatgt agacccgcag ctggtggggc cgtgcataacc      900
cggggcttgc acttcgcctg cgatatctac atttgggccc ctctggotgg tacttgccgg      960
gtctcgctgc tttcactcgt gatcaactt tactgtaaagc ggggtggaa gaagctgtg      1020
tacatcttta agcaaccctt catgaggcct gtgcagacta ctcaagagga ggacggctgt      1080
tcatgcgggt tcccgagga ggaggaaggc ggctgcgaac tgcgcgtgaa attcagccgc      1140
agcgcagatg ctccagccta caagcagggg cagaaccacg tctacaacga actcaatctt      1200
ggtcggagag aggatgtacga cgtgtggac aacgggagag gacgggaccc agaaatggc      1260
gggaagccgc gcagaaaagaa tccccaaagag ggctgtaca acgagctcca aaaggataag      1320
atggcagaag cctatagcga gattggatg aaaggggaac gcagaagagg caaaggccac      1380
gacggactgt accaggact cagcacccgcc accaaggaca cctatgacgc tcttcacatg      1440
caggccctgc cgcctcg      1458

```

```

<210> SEQ ID NO 308
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

```

```
<400> SEQUENCE: 308
```

```
Leu Ala Glu Ala Ala Ala Lys
1           5
```

```

<210> SEQ ID NO 309
<211> LENGTH: 284
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polypeptide

```

```
<400> SEQUENCE: 309
```

```

Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile
1           5           10          15
Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His
20          25          30

```

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Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln  
     35                        40                        45  
 Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu  
     50                        55                        60  
 Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val  
     65                        70                        75                        80  
 Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile  
     85                        90                        95  
 Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn  
     100                       105                       110  
 Thr Ser Ile Thr Cys Pro Pro Met Ser Val Glu His Ala Asp Ile  
     115                       120                       125  
 Trp Val Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn  
     130                       135                       140  
 Ser Gly Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val  
     145                       150                       155                       160  
 Leu Asn Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys  
     165                       170                       175  
 Cys Ile Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser  
     180                       185                       190  
 Thr Val Thr Thr Ala Gly Val Thr Pro Gln Pro Glu Ser Leu Ser Pro  
     195                       200                       205  
 Ser Gly Lys Glu Pro Ala Ala Ser Ser Pro Ser Ser Asn Asn Thr Ala  
     210                       215                       220  
 Ala Thr Thr Ala Ala Ile Val Pro Gly Ser Gln Leu Met Pro Ser Lys  
     225                       230                       235                       240  
 Ser Pro Ser Thr Gly Thr Thr Glu Ile Ser Ser His Glu Ser Ser His  
     245                       250                       255  
 Gly Thr Pro Ser Gln Thr Thr Ala Lys Asn Trp Glu Leu Thr Ala Ser  
     260                       265                       270  
 Ala Ser His Gln Pro Pro Gly Val Tyr Pro Gln Gly  
     275                       280

<210> SEQ ID NO 310  
 <211> LENGTH: 7  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 310

Gly Val Ser Leu Pro Asp Tyr  
     1                               5

<210> SEQ ID NO 311  
 <211> LENGTH: 5  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

&lt;400&gt; SEQUENCE: 311

Trp Gly Ser Glu Thr  
     1                               5

&lt;210&gt; SEQ ID NO 312

-continued

<211> LENGTH: 8  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 312

Gly Val Ser Leu Pro Asp Tyr Gly  
1 5

<210> SEQ ID NO 313  
<211> LENGTH: 7  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 313

Ile Trp Gly Ser Glu Thr Thr  
1 5

<210> SEQ ID NO 314  
<211> LENGTH: 14  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 314

Ala Lys His Tyr Tyr Tyr Gly Ser Tyr Ala Met Asp Tyr  
1 5 10

<210> SEQ ID NO 315  
<211> LENGTH: 360  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 315

cagggtccaa	tccaagaaag	cgacgggggt	cttgtgaagc	catcagaaac	tctttcactg	60
acttgtactg	tgagcggagt	gtctctcccc	gattacgggg	tgtcttggat	cagacagcc	120
ccggggaaagg	gtctggaatg	gattggagtg	atttggggct	ctgagactac	ttactacaa	180
tcatccctca	agtcacgcgt	caccatctca	aaggacaact	ctaagaatca	ggtgtcactg	240
aaactgtcat	ctgtgaccgc	agccgacacc	gccgtgtact	attgcgctaa	gcattactat	300
tatggcggga	gtacgcaat	ggattactgg	ggacaggta	ctctggcac	cgtgtccagc	360

<210> SEQ ID NO 316  
<211> LENGTH: 7  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 316

Ser Gln Asp Ile Ser Lys Tyr  
1 5

<210> SEQ ID NO 317

-continued

<211> LENGTH: 3  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 317

His Thr Ser  
1

<210> SEQ ID NO 318  
<211> LENGTH: 6  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 318

Gly Asn Thr Leu Pro Tyr  
1 5

<210> SEQ ID NO 319  
<211> LENGTH: 6  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 319

Gln Asp Ile Ser Lys Tyr  
1 5

<210> SEQ ID NO 320  
<211> LENGTH: 321  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 320

gaaaattgtga tgacccttgtc acceggccact ctttagccctt caccgggtga gcgcgcaacc	60
ctgtcttgca gagcctccca agacatctca aaatacctta attggtatca acagaagccc	120
ggacaggctc ctgccttct gatctaccac accagccggc tccattctgg aatccctgcc	180
aggttcagcg gtagcggatc tgggaccgac tacaccctca ctatcagctc actgcagcca	240
gaggacttcg ctgtctatTT ctgtcagcaa gggAACACCC tgccctacac ctttggacag	300
ggcaccaAGC tcgagattaa a	321

<210> SEQ ID NO 321  
<211> LENGTH: 491  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 321

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu	
1 5 10 15	
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr	
20 25 30	

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Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Cys Leu Glu Trp Ile  
35 40 45

Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Gln Ser Ser Leu Lys  
50 55 60

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

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala  
85 90 95

Lys His Tyr Tyr Tyr Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln  
100 105 110

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser Gln Ser Ala  
115 120 125

Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr  
130 135 140

Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val  
145 150 155 160

Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr  
165 170 175

Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser  
180 185 190

Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu  
195 200 205

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

Tyr Val Phe Gly Ser Gly Thr Lys Val Thr Val Leu Gly Gly Gly  
225 230 235 240

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser  
245 250 255

Gln Val Gln Leu Gln Glu Ser Gly Gly Val Val Gln Pro Gly Arg  
260 265 270

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr  
275 280 285

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
290 295 300

Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val  
305 310 315 320

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr  
325 330 335

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
340 345 350

Gly Gly Ser Gly Tyr Ala Leu His Asp Asp Tyr Tyr Gly Leu Asp Val  
355 360 365

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser  
370 375 380

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly  
385 390 395 400

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr  
405 410 415

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile  
420 425 430

Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly  
435 440 445

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-continued

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro  
450 455 460

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr  
465 470 475 480

Thr Phe Gly Cys Gly Thr Lys Leu Glu Ile Lys  
485 490

&lt;210&gt; SEQ ID NO 322

&lt;211&gt; LENGTH: 491

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 322

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

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

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile  
35 40 45

Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly  
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro  
65 70 75 80

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr  
85 90 95

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

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr  
130 135 140

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
145 150 155 160

Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val  
165 170 175

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr  
180 185 190

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
195 200 205

Gly Gly Ser Gly Tyr Ala Leu His Asp Asp Tyr Tyr Gly Leu Asp Val  
210 215 220

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Ser Gly Ser  
225 230 235 240

Gly Gly Gly Ser Gly Gly Ser Gly Gly Gly Ser Gln  
245 250 255

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

Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn  
275 280 285

Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met  
290 295 300

Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe Ser  
305 310 315 320

-continued

Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln  
325 330 335

Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser Ser  
340 345 350

Thr Leu Tyr Val Phe Gly Ser Gly Thr Lys Val Thr Val Leu Gly Gly  
355 360 365

Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys  
370 375 380

Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu  
385 390 395 400

Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Cys Leu  
405 410 415

Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Gln Ser  
420 425 430

Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln  
435 440 445

Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr  
450 455 460

Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Ser Tyr Ala Met Asp Tyr  
465 470 475 480

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser  
485 490

<210> SEQ ID NO 323  
<211> LENGTH: 491  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 323

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr  
20 25 30

Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Cys Leu Glu Trp Ile  
35 40 45

Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Gln Ser Ser Leu Lys  
50 55 60

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

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala  
85 90 95

Lys His Tyr Tyr Tyr Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln  
100 105 110

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

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

Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Gly Met His  
145 150 155 160

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

Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys Gly Arg

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180

185

190

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

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

Gly Tyr Ala Leu His Asp Asp Tyr Tyr Gly Leu Asp Val Trp Gly Gln  
225 230 235 240

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly Gly  
245 250 255

Gly Ser Gly Gly Ser Gly Gly Ser Gln Ser Ala Leu  
260 265 270

Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile  
275 280 285

Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser  
290 295 300

Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Asp  
305 310 315 320

Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys  
325 330 335

Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp  
340 345 350

Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser Ser Thr Leu Tyr  
355 360 365

Val Phe Gly Ser Gly Thr Lys Val Thr Val Leu Gly Gly Gly Ser  
370 375 380

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly  
385 390 395 400

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr  
405 410 415

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile  
420 425 430

Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly  
435 440 445

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro  
450 455 460

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr  
465 470 475 480

Thr Phe Gly Cys Gly Thr Lys Leu Glu Ile Lys  
485 490

&lt;210&gt; SEQ ID NO: 324

&lt;211&gt; LENGTH: 491

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 324

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

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

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile  
35 40 45

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Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly  
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro  
65 70 75 80

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr  
85 90 95

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

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

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr  
130 135 140

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu  
145 150 155 160

Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe  
165 170 175

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu  
180 185 190

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser  
195 200 205

Ser Thr Leu Tyr Val Phe Gly Ser Gly Thr Lys Val Thr Val Leu Gly  
210 215 220

Gly Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly  
225 230 235 240

Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Gly Val Val Gln  
245 250 255

Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe  
260 265 270

Ser Ser Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu  
275 280 285

Glu Trp Val Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala  
290 295 300

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn  
305 310 315 320

Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val  
325 330 335

Tyr Tyr Cys Gly Gly Ser Gly Tyr Ala Leu His Asp Asp Tyr Tyr Gly  
340 345 350

Leu Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly  
355 360 365

Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys  
370 375 380

Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu  
385 390 395 400

Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Cys Leu  
405 410 415

Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Gly Ser  
420 425 430

Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln  
435 440 445

Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr  
450 455 460

Tyr Cys Ala Lys His Tyr Tyr Gly Ser Tyr Ala Met Asp Tyr

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-continued

465                    470                    475                    480

Trp Gly Gln Gly Thr Leu Val Thr Val Ser

<210> SEQ ID NO 325  
<211> LENGTH: 491  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 325

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

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

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

Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val  
50 55 60

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

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

Gly Gly Ser Gly Tyr Ala Leu His Asp Asp Tyr Tyr Gly Leu Asp Val  
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser  
           115                  120                  125

Glu	Ile	Val	Met	Thr	Gln	Ser	Pro	Ala	Thr	Leu	Ser	Leu	Ser	Pro	Gly
130					135						140				

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr  
145 150 155 160

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile  
165 170 175

Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly  
                  180                 185                 190

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro  
195 200 205

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr  
 210 215 220

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser  
225 230 235 240

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln  
245 250 255

Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr  
360 365 370

Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly

Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly  
290 295 300

Val	Ile	Trp	Gly	Ser	Glu	Thr	Thr	Tyr	Tyr	Gln	Ser	Ser	Leu	Lys	Ser
305					310					315					320

Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys  
325 330 335

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-continued

Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys  
 340 345 350  
 His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly  
 355 360 365  
 Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser Gln Ser Ala Leu  
 370 375 380  
 Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile  
 385 390 395 400  
 Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser  
 405 410 415  
 Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Asp  
 420 425 430  
 Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys  
 435 440 445  
 Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp  
 450 455 460  
 Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser Ser Thr Leu Tyr  
 465 470 475 480  
 Val Phe Gly Cys Gly Thr Lys Val Thr Val Leu  
 485 490

<210> SEQ ID NO 326  
 <211> LENGTH: 491  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 polypeptide

<400> SEQUENCE: 326

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

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr  
 20 25 30

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

Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe  
 50 55 60

Ser	Gly	Ser	Lys	Ser	Gly	Asn	Thr	Ala	Ser	Leu	Thr	Ile	Ser	Gly	Leu
65						70				75				80	

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser  
 85 90 95

Ser	Thr	Leu	Tyr	Val	Phe	Gly	Cys	Gly	Thr	Lys	Val	Thr	Val	Leu	Gly
100					105				110						

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

Lys	Pro	Ser	Glu	Thr	Leu	Ser	Leu	Thr	Cys	Thr	Val	Ser	Gly	Val	Ser
130						135					140				

Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly  
 145 150 155 160

Leu	Glu	Trp	Ile	Gly	Val	Ile	Trp	Gly	Ser	Glu	Thr	Thr	Tyr	Tyr	Gln
165						170					175				

Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn  
 180 185 190

Gln	Val	Ser	Leu	Lys	Leu	Ser	Ser	Val	Thr	Ala	Ala	Asp	Thr	Ala	Val
195						200					205				

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Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp  
 210 215 220

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

Ser Gly Gly Gly Ser Gly Gly Ser Gly Gly Gly Ser  
 245 250 255

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly  
 260 265 270

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr  
 275 280 285

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile  
 290 295 300

Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly  
 305 310 315 320

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro  
 325 330 335

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr  
 340 345 350

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Ser  
 355 360 365

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg  
 370 375 380

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr  
 385 390 395 400

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Cys Leu Glu Trp Val  
 405 410 415

Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val  
 420 425 430

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr  
 435 440 445

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
 450 455 460

Gly Gly Ser Gly Tyr Ala Leu His Asp Asp Tyr Tyr Gly Leu Asp Val  
 465 470 475 480

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser  
 485 490

<210> SEQ\_ID NO 327  
 <211> LENGTH: 491  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 327

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

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

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

Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val  
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

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65	70	75	80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys			
85	90	95	
Gly Gly Ser Gly Tyr Ala Leu His Asp Asp Tyr Tyr Gly Leu Asp Val			
100	105	110	
Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser			
115	120	125	
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu			
130	135	140	
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr			
145	150	155	160
Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile			
165	170	175	
Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Gln Ser Ser Leu Lys			
180	185	190	
Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln Val Ser Leu			
195	200	205	
Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala			
210	215	220	
Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln			
225	230	235	240
Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly Gly			
245	250	255	
Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Glu Ile Val Met			
260	265	270	
Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr			
275	280	285	
Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr			
290	295	300	
Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr His Thr Ser			
305	310	315	320
Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly			
325	330	335	
Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala			
340	345	350	
Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gln			
355	360	365	
Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Ser Gln Ser Ala Leu			
370	375	380	
Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile			
385	390	395	400
Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser			
405	410	415	
Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Asp			
420	425	430	
Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys			
435	440	445	
Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp			
450	455	460	
Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser Ser Thr Leu Tyr			
465	470	475	480
Val Phe Gly Cys Gly Thr Lys Val Thr Val Leu			
485	490		

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-continued

<210> SEQ\_ID NO 328  
<211> LENGTH: 491  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 328

Gln	Ser	Ala	Leu	Thr	Gln	Pro	Ala	Ser	Val	Ser	Gly	Ser	Pro	Gly	Gln
1															
															10
															15

Ser	Ile	Thr	Ile	Ser	Cys	Thr	Gly	Thr	Ser	Ser	Asp	Val	Gly	Gly	Tyr
															20
															25
															30

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

Met	Ile	Tyr	Asp	Val	Ser	Asn	Arg	Pro	Ser	Gly	Val	Ser	Asn	Arg	Phe
															50
															55
															60

Ser	Gly	Ser	Lys	Ser	Gly	Asn	Thr	Ala	Ser	Leu	Thr	Ile	Ser	Gly	Leu
															65
															70
															75
															80

Gln	Ala	Glu	Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Ser	Ser	Tyr	Thr	Ser	Ser
															85
															90
															95

Ser	Thr	Leu	Tyr	Val	Phe	Gly	Cys	Gly	Thr	Lys	Val	Thr	Val	Leu	Gly
															100
															105
															110

Gly	Gly	Ser	Glu	Ile	Val	Met	Thr	Gln	Ser	Pro	Ala	Thr	Leu	Ser	
															115
															120
															125

Leu	Ser	Pro	Gly	Glu	Arg	Ala	Thr	Leu	Ser	Cys	Arg	Ala	Ser	Gln	Asp
															130
															135
															140

Ile	Ser	Lys	Tyr	Leu	Asn	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro
															145
															150
															155
															160

Arg	Leu	Leu	Ile	Tyr	His	Thr	Ser	Arg	Leu	His	Ser	Gly	Ile	Pro	Ala
															165
															170
															175

Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Tyr	Thr	Leu	Thr	Ile	Ser
															180
															185
															190

Ser	Leu	Gln	Pro	Glu	Asp	Phe	Ala	Val	Tyr	Phe	Cys	Gln	Gln	Gly	Asn
															195
															200
															205

Thr	Leu	Pro	Tyr	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Lys	Gly
															210
															215
															220

Gly	Gly	Ser	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly
															225
															230
															235
															240

Gly	Gly	Ser	Gln	Val	Gln	Leu	Gln	Glu	Ser	Gly	Pro	Gly	Leu	Val	Lys
															245
															250
															255

Pro	Ser	Glu	Thr	Leu	Ser	Leu	Thr	Cys	Thr	Val	Ser	Gly	Val	Ser	Leu
															260
															265
															270

Pro	Asp	Tyr	Gly	Val	Ser	Trp	Ile	Arg	Gln	Pro	Pro	Gly	Lys	Gly	Leu
															275
															280
															285

Glu	Trp	Ile	Gly	Val	Ile	Trp	Gly	Ser	Glu	Thr	Thr	Tyr	Tyr	Gln	Ser
															290
															295
															300

Ser	Leu	Lys	Ser	Arg	Val	Thr	Ile	Ser	Lys	Asp	Asn	Ser	Lys	Asn	Gln
															305
															310
															315
															320

Val	Ser	Leu	Lys	Ser	Leu	Ser	Ser	Val	Thr	Ala	Ala	Asp	Thr	Ala	Val	Tyr
															325	
															330	
															335	

Tyr	Cys	Ala	Lys	His	Tyr	Tyr	Tyr	Gly	Gly	Ser	Tyr	Ala	Met	Asp	Tyr
															340
															345
															350

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser

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355                    360                    365

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg  
 370                    375                    380

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr  
 385                    390                    395                    400

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Cys Leu Glu Trp Val  
 405                    410                    415

Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val  
 420                    425                    430

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr  
 435                    440                    445

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
 450                    455                    460

Gly Gly Ser Gly Tyr Ala Leu His Asp Asp Tyr Tyr Gly Leu Asp Val  
 465                    470                    475                    480

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser  
 485                    490

&lt;210&gt; SEQ ID NO 329

&lt;211&gt; LENGTH: 485

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 329

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr  
 20                    25                    30

Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Cys Leu Glu Trp Ile  
 35                    40                    45

Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Gln Ser Ser Leu Lys  
 50                    55                    60

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

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala  
 85                    90                    95

Lys His Tyr Tyr Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln  
 100                    105                    110

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser Asp Ile Gln  
 115                    120                    125

Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val  
 130                    135                    140

Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn Trp  
 145                    150                    155                    160

Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala  
 165                    170                    175

Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser  
 180                    185                    190

Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe  
 195                    200                    205

Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Leu Thr Phe Gly  
 210                    215                    220

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Gln Gly Thr Lys Val Glu Ile Lys Gly Gly Gly Ser Gly Gly  
225                    230                    235                    240

Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Glu Val Gln Leu  
245                    250                    255

Leu Glu Ser Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu  
260                    265                    270

Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Ala Met Ser Trp  
275                    280                    285

Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Ala Ile Ser  
290                    295                    300

Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe  
305                    310                    315                    320

Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn  
325                    330                    335

Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Arg Glu  
340                    345                    350

Trp Trp Gly Glu Ser Trp Leu Phe Asp Tyr Trp Gly Gln Gly Thr Leu  
355                    360                    365

Val Thr Val Ser Ser Gly Gly Gly Ser Glu Ile Val Met Thr Gln  
370                    375                    380

Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser  
385                    390                    395                    400

Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln  
405                    410                    415

Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu  
420                    425                    430

His Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Thr Asp  
435                    440                    445

Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr  
450                    455                    460

Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr Phe Gly Cys Gly Thr  
465                    470                    475                    480

Lys Leu Glu Ile Lys  
485

<210> SEQ ID NO 330  
<211> LENGTH: 485  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 330

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

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

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

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

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

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

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Ala Arg Arg Glu Trp Trp Gly Glu Ser Trp Leu Phe Asp Tyr Trp Gly  
 100 105 110  
 Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser Glu Ile  
 115 120 125  
 Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg  
 130 135 140  
 Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu Asn  
 145 150 155 160  
 Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr His  
 165 170 175  
 Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly  
 180 185 190  
 Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp  
 195 200 205  
 Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr Phe  
 210 215 220  
 Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Ser Gly Gly  
 225 230 235 240  
 Gly Gly Ser Gly Gly Ser Gly Gly Gly Ser Gln Val Gln  
 245 250 255  
 Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr Leu Ser  
 260 265 270  
 Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser  
 275 280 285  
 Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly Val Ile  
 290 295 300  
 Trp Gly Ser Glu Thr Thr Tyr Tyr Gln Ser Ser Leu Lys Ser Arg Val  
 305 310 315 320  
 Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys Leu Ser  
 325 330 335  
 Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys His Tyr  
 340 345 350  
 Tyr Tyr Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu  
 355 360 365  
 Val Thr Val Ser Ser Gly Gly Gly Ser Asp Ile Gln Met Thr Gln  
 370 375 380  
 Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr  
 385 390 395 400  
 Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn Trp Tyr Gln Gln  
 405 410 415  
 Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Ser Leu  
 420 425 430  
 Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp  
 435 440 445  
 Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr  
 450 455 460  
 Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Leu Thr Phe Gly Cys Gly Thr  
 465 470 475 480  
 Lys Val Glu Ile Lys  
 485

<210> SEQ ID NO 331  
 <211> LENGTH: 120

-continued

<212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 331

```

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr
20          25          30

Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Cys Leu Glu Trp Ile
35          40          45

Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Gln Ser Ser Leu Lys
50          55          60

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

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85          90          95

Lys His Tyr Tyr Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln
100         105         110

Gly Thr Leu Val Thr Val Ser Ser
115         120
  
```

<210> SEQ ID NO 332  
 <211> LENGTH: 107  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 332

```

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

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

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35          40          45

Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly
50          55          60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65          70          75          80

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr
85          90          95

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

<210> SEQ ID NO 333  
 <211> LENGTH: 123  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 333

```

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
  
```

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-continued

20                    25                    30

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

Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val  
 50                    55                    60

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

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

Gly Gly Ser Gly Tyr Ala Leu His Asp Asp Tyr Tyr Gly Leu Asp Val  
 100                  105                  110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser  
 115                  120

&lt;210&gt; SEQ ID NO 334

&lt;211&gt; LENGTH: 111

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 334

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

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr  
 20                  25                  30

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

Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe  
 50                  55                  60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu  
 65                  70                  75                  80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser  
 85                  90                  95

Ser Thr Leu Tyr Val Phe Gly Cys Gly Thr Lys Val Thr Val Leu  
 100                105                110

&lt;210&gt; SEQ ID NO 335

&lt;211&gt; LENGTH: 121

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 335

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

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

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

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

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

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

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-continued

85 90 95

Ala Arg Arg Glu Trp Trp Gly Glu Ser Trp Leu Phe Asp Tyr Trp Gly  
 100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser  
 115 120

<210> SEQ ID NO 336  
 <211> LENGTH: 107  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 336

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr  
 20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile  
 35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly  
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro  
 65 70 75 80

Glu Asp Phe Ala Thr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Leu  
 85 90 95

Thr Phe Gly Cys Gly Thr Lys Val Glu Ile Lys  
 100 105

<210> SEQ ID NO 337  
 <211> LENGTH: 135  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 337

accactaccc cagcacccgag gccacccacc cccggctctca ccatacgccctc ccagectctg 60

tccctgcgtc cggaggcatg tagaccgcga gctgggtgggg ccgtgcatac ccggggtctt 120

gacttcgcct gcatat 135

<210> SEQ ID NO 338  
 <211> LENGTH: 72  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

&lt;400&gt; SEQUENCE: 338

atctacattt gggccccctct ggctggtaact tgcggggtcc tgctgctttc actcgtgatc 60

actctttact gt 72

<210> SEQ ID NO 339  
 <211> LENGTH: 714  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

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polypeptide

&lt;400&gt; SEQUENCE: 339

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

Thr	Leu	Ser	Leu	Thr	Cys	Thr	Val	Ser	Gly	Val	Ser	Leu	Pro	Asp	Tyr
	20				25							30			

Gly	Val	Ser	Trp	Ile	Arg	Gln	Pro	Pro	Gly	Lys	Cys	Leu	Glu	Trp	Ile
	35				40					45					

Gly	Val	Ile	Trp	Gly	Ser	Glu	Thr	Thr	Tyr	Tyr	Gln	Ser	Ser	Leu	Lys
	50			55			60								

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

Lys	Leu	Ser	Ser	Val	Thr	Ala	Ala	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	Ala
	85				90					95					

Lys	His	Tyr	Tyr	Tyr	Gly	Gly	Ser	Tyr	Ala	Met	Asp	Tyr	Trp	Gly	Gln
	100				105					110					

Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	Ser	Gln	Ser	Ala
	115				120			125						

Leu	Thr	Gln	Pro	Ala	Ser	Val	Ser	Gly	Ser	Pro	Gly	Gln	Ser	Ile	Thr
	130				135			140							

Ile	Ser	Cys	Thr	Gly	Thr	Ser	Ser	Asp	Val	Gly	Gly	Tyr	Asn	Tyr	Val
145				150				155			160				

Ser	Trp	Tyr	Gln	Gln	His	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Met	Ile	Tyr
	165				170			175							

Asp	Val	Ser	Asn	Arg	Pro	Ser	Gly	Val	Ser	Asn	Arg	Phe	Ser	Gly	Ser
	180				185			190							

Lys	Ser	Gly	Asn	Thr	Ala	Ser	Leu	Thr	Ile	Ser	Gly	Leu	Gln	Ala	Glu
	195				200			205							

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

Tyr	Val	Phe	Gly	Ser	Gly	Thr	Lys	Val	Thr	Leu	Gly	Gly	Gly	
225		230			235			240						

Ser	Gly	Gly	Ser	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser			
	245			250			255							

Gln	Val	Gln	Leu	Gln	Glu	Ser	Gly	Gly	Val	Val	Gln	Pro	Gly	Arg
	260				265			270						

Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Ser	Tyr
	275			280			285								

Gly	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
	290			295			300								

Ala	Val	Ile	Ser	Tyr	Asp	Gly	Ser	Asn	Lys	Tyr	Tyr	Ala	Asp	Ser	Val
	305			310			315			320					

Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr
	325			330			335								

Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
	340			345			350								

Gly	Gly	Ser	Gly	Tyr	Ala	Leu	His	Asp	Asp	Tyr	Tyr	Gly	Leu	Asp	Val
	355			360			365								

Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	Ser	
	370			375			380								

Glu	Ile	Val	Met	Thr	Gln	Ser	Pro	Ala	Thr	Leu	Ser	Leu	Ser	Pro	Gly
	385			390			395			400					

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Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr  
405 410 415

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile  
420 425 430

Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly  
435 440 445

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro  
450 455 460

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr  
465 470 475 480

Thr Phe Gly Cys Gly Thr Lys Leu Glu Ile Lys Thr Thr Pro Ala  
485 490 495

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser  
500 505 510

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr  
515 520 525

Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala  
530 535 540

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys  
545 550 555 560

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met  
565 570 575

Arg Pro Val Gln Thr Thr Gln Glu Asp Gly Cys Ser Cys Arg Phe  
580 585 590

Pro Glu Glu Glu Gly Cys Glu Leu Arg Val Lys Phe Ser Arg  
595 600 605

Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn  
610 615 620

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg  
625 630 635 640

Arg Gly Arg Asp Pro Glu Met Gly Lys Pro Arg Arg Lys Asn Pro  
645 650 655

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala  
660 665 670

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His  
675 680 685

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp  
690 695 700

Ala Leu His Met Gln Ala Leu Pro Pro Arg  
705 710

<210> SEQ ID NO 340  
<211> LENGTH: 714  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 340

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

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

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile  
35 40 45

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Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly  
 50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro  
 65 70 75 80

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr  
 85 90 95

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

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr  
 130 135 140

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 145 150 155 160

Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val  
 165 170 175

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr  
 180 185 190

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
 195 200 205

Gly Gly Ser Gly Tyr Ala Leu His Asp Asp Tyr Tyr Gly Leu Asp Val  
 210 215 220

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser  
 225 230 235 240

Gly Gly Gly Ser Gly Gly Ser Gly Gly Gly Ser Gln  
 245 250 255

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

Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn  
 275 280 285

Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met  
 290 295 300

Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe Ser  
 305 310 315 320

Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln  
 325 330 335

Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser Ser  
 340 345 350

Thr Leu Tyr Val Phe Gly Ser Gly Thr Lys Val Thr Val Leu Gly Gly  
 355 360 365

Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys  
 370 375 380

Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu  
 385 390 395 400

Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Cys Leu  
 405 410 415

Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Gln Ser  
 420 425 430

Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln  
 435 440 445

Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr  
 450 455 460

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-continued

Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr  
465 470 475 480

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Thr Thr Thr Pro Ala  
485 490 495

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser  
500 505 510

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr  
515 520 525

Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala  
530 535 540

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys  
545 550 555 560

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met  
565 570 575

Arg Pro Val Gln Thr Thr Gln Glu Asp Gly Cys Ser Cys Arg Phe  
580 585 590

Pro Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg  
595 600 605

Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn  
610 615 620

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg  
625 630 635 640

Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro  
645 650 655

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala  
660 665 670

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His  
675 680 685

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp  
690 695 700

Ala Leu His Met Gln Ala Leu Pro Pro Arg  
705 710

<210> SEQ ID NO 341  
<211> LENGTH: 714  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 341

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr  
20 25 30

Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Cys Leu Glu Trp Ile  
35 40 45

Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Gln Ser Ser Leu Lys  
50 55 60

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

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala  
85 90 95

Lys His Tyr Tyr Tyr Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln  
100 105 110

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-continued

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

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

Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Gly Met His  
145 150 155 160

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

Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys Gly Arg  
180 185 190

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

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

Gly Tyr Ala Leu His Asp Asp Tyr Tyr Gly Leu Asp Val Trp Gly Gln  
225 230 235 240

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly  
245 250 255

Gly Ser Gly Gly Ser Gly Gly Ser Gln Ser Ala Leu  
260 265 270

Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile  
275 280 285

Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser  
290 295 300

Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Asp  
305 310 315 320

Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys  
325 330 335

Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp  
340 345 350

Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser Ser Thr Leu Tyr  
355 360 365

Val Phe Gly Ser Gly Thr Lys Val Thr Val Leu Gly Gly Gly Ser  
370 375 380

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly  
385 390 395 400

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr  
405 410 415

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile  
420 425 430

Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly  
435 440 445

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro  
450 455 460

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr  
465 470 475 480

Thr Phe Gly Cys Gly Thr Lys Leu Glu Ile Lys Thr Thr Pro Ala  
485 490 495

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser  
500 505 510

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr  
515 520 525

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Arg	Gly	Leu	Asp	Phe	Ala	Cys	Asp	Ile	Tyr	Ile	Trp	Ala	Pro	Leu	Ala
530					535						540				

Gly	Thr	Cys	Gly	Val	Leu	Leu	Leu	Ser	Leu	Val	Ile	Thr	Leu	Tyr	Cys
545					550						555			560	

Lys	Arg	Gly	Arg	Lys	Lys	Leu	Leu	Tyr	Ile	Phe	Lys	Gln	Pro	Phe	Met
565						570					575				

Arg	Pro	Val	Gln	Thr	Thr	Gln	Glu	Glu	Asp	Gly	Cys	Ser	Cys	Arg	Phe
580						585					590				

Pro	Glu	Glu	Glu	Gly	Gly	Cys	Glu	Leu	Arg	Val	Lys	Phe	Ser	Arg
595					600					605				

Ser	Ala	Asp	Ala	Pro	Ala	Tyr	Lys	Gln	Gly	Gln	Asn	Gln	Leu	Tyr	Asn
610					615					620					

Glu	Leu	Asn	Leu	Gly	Arg	Arg	Glu	Glu	Tyr	Asp	Val	Leu	Asp	Lys	Arg
625					630					635			640		

Arg	Gly	Arg	Asp	Pro	Glu	Met	Gly	Gly	Lys	Pro	Arg	Arg	Lys	Asn	Pro
645					650					655					

Gln	Glu	Gly	Leu	Tyr	Asn	Glu	Leu	Gln	Lys	Asp	Lys	Met	Ala	Glu	Ala
660					665					670					

Tyr	Ser	Glu	Ile	Gly	Met	Lys	Gly	Glu	Arg	Arg	Arg	Gly	Lys	Gly	His
675					680					685					

Asp	Gly	Leu	Tyr	Gln	Gly	Leu	Ser	Thr	Ala	Thr	Lys	Asp	Thr	Tyr	Asp
690					695					700					

Ala	Leu	His	Met	Gln	Ala	Leu	Pro	Pro	Arg
705					710				

&lt;210&gt; SEQ ID NO 342

&lt;211&gt; LENGTH: 714

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 342

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

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

Leu	Asn	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Leu	Leu	Ile
35				40					45						

Tyr	His	Thr	Ser	Arg	Leu	His	Ser	Gly	Ile	Pro	Ala	Arg	Phe	Ser	Gly
50				55					60						

Ser	Gly	Ser	Gly	Thr	Asp	Tyr	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
65				70					75			80			

Glu	Asp	Phe	Ala	Val	Tyr	Phe	Cys	Gln	Gln	Gly	Asn	Thr	Leu	Pro	Tyr
85				90					95						

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

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

Ser	Ile	Thr	Ile	Ser	Cys	Thr	Gly	Thr	Ser	Ser	Asp	Val	Gly	Gly	Tyr
130				135					140						

Asn	Tyr	Val	Ser	Trp	Tyr	Gln	Gln	His	Pro	Gly	Lys	Ala	Pro	Lys	Leu
145				150					155			160			

Met	Ile	Tyr	Asp	Val	Ser	Asn	Arg	Pro	Ser	Gly	Val	Ser	Asn	Arg	Phe
165				170					175						

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Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu  
 180 185 190  
 Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser  
 195 200 205  
 Ser Thr Leu Tyr Val Phe Gly Ser Gly Thr Lys Val Thr Val Leu Gly  
 210 215 220  
 Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly  
 225 230 235 240  
 Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Val Val Gln  
 245 250 255  
 Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe  
 260 265 270  
 Ser Ser Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu  
 275 280 285  
 Glu Trp Val Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala  
 290 295 300  
 Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn  
 305 310 315 320  
 Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val  
 325 330 335  
 Tyr Tyr Cys Gly Gly Ser Gly Tyr Ala Leu His Asp Asp Tyr Tyr Gly  
 340 345 350  
 Leu Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly  
 355 360 365  
 Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys  
 370 375 380  
 Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu  
 385 390 395 400  
 Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Cys Leu  
 405 410 415  
 Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Gln Ser  
 420 425 430  
 Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln  
 435 440 445  
 Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr  
 450 455 460  
 Tyr Cys Ala Lys His Tyr Tyr Gly Ser Tyr Ala Met Asp Tyr  
 465 470 475 480  
 Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Thr Thr Pro Ala  
 485 490 495  
 Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser  
 500 505 510  
 Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr  
 515 520 525  
 Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala  
 530 535 540  
 Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys  
 545 550 555 560  
 Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met  
 565 570 575  
 Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe  
 580 585 590

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Pro Glu Glu Glu Glu Gly Cys Glu Leu Arg Val Lys Phe Ser Arg  
595 600 605

Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn  
610 615 620

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg  
625 630 635 640

Arg Gly Arg Asp Pro Glu Met Gly Lys Pro Arg Arg Lys Asn Pro  
645 650 655

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala  
660 665 670

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His  
675 680 685

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp  
690 695 700

Ala Leu His Met Gln Ala Leu Pro Pro Arg  
705 710

&lt;210&gt; SEQ ID NO 343

&lt;211&gt; LENGTH: 714

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 343

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

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

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

Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val  
50 55 60

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

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

Gly Gly Ser Gly Tyr Ala Leu His Asp Asp Tyr Tyr Gly Leu Asp Val  
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser  
115 120 125

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly  
130 135 140

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr  
145 150 155 160

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile  
165 170 175

Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly  
180 185 190

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro  
195 200 205

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr  
210 215 220

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Ser  
225 230 235 240

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Gly Gly Gly Ser Gly Gly Ser Gly Gly Ser Gln  
245 250 255

Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr  
260 265 270

Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly  
275 280 285

Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly  
290 295 300

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Gln Ser Ser Leu Lys Ser  
305 310 315 320

Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys  
325 330 335

Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys  
340 345 350

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly  
355 360 365

Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser Gln Ser Ala Leu  
370 375 380

Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile  
385 390 395 400

Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser  
405 410 415

Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Asp  
420 425 430

Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys  
435 440 445

Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp  
450 455 460

Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser Ser Thr Leu Tyr  
465 470 475 480

Val Phe Gly Cys Gly Thr Lys Val Thr Val Leu Thr Thr Pro Ala  
485 490 495

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser  
500 505 510

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr  
515 520 525

Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala  
530 535 540

Gly Thr Cys Gly Val Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys  
545 550 555 560

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met  
565 570 575

Arg Pro Val Gln Thr Thr Gln Glu Asp Gly Cys Ser Cys Arg Phe  
580 585 590

Pro Glu Glu Glu Gly Cys Glu Leu Arg Val Lys Phe Ser Arg  
595 600 605

Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn  
610 615 620

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg  
625 630 635 640

Arg Gly Arg Asp Pro Glu Met Gly Lys Pro Arg Arg Lys Asn Pro  
645 650 655

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**699****700**

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Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala  
 660 665 670

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His  
 675 680 685

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp  
 690 695 700

Ala Leu His Met Gln Ala Leu Pro Pro Arg  
 705 710

&lt;210&gt; SEQ ID NO 344

&lt;211&gt; LENGTH: 714

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 344

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

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr  
 20 25 30

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

Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe  
 50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu  
 65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser  
 85 90 95

Ser Thr Leu Tyr Val Phe Gly Cys Gly Thr Lys Val Thr Val Leu Gly  
 100 105 110

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

Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser  
 130 135 140

Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly  
 145 150 155 160

Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Gln  
 165 170 175

Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn  
 180 185 190

Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val  
 195 200 205

Tyr Tyr Cys Ala Lys His Tyr Tyr Gly Ser Tyr Ala Met Asp  
 210 215 220

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

Ser Gly Gly Gly Ser Gly Gly Ser Gly Gly Gly Ser  
 245 250 255

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly  
 260 265 270

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr  
 275 280 285

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile  
 290 295 300

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-continued

Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly  
 305 310 315 320

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro  
 325 330 335

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr  
 340 345 350

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Ser  
 355 360 365

Gln Val Gln Leu Gln Glu Ser Gly Gly Val Val Gln Pro Gly Arg  
 370 375 380

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr  
 385 390 395 400

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Cys Leu Glu Trp Val  
 405 410 415

Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val  
 420 425 430

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr  
 435 440 445

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
 450 455 460

Gly Gly Ser Gly Tyr Ala Leu His Asp Asp Tyr Tyr Gly Leu Asp Val  
 465 470 475 480

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Thr Thr Pro Ala  
 485 490 495

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser  
 500 505 510

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr  
 515 520 525

Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala  
 530 535 540

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys  
 545 550 555 560

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met  
 565 570 575

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe  
 580 585 590

Pro Glu Glu Glu Gly Cys Glu Leu Arg Val Lys Phe Ser Arg  
 595 600 605

Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn  
 610 615 620

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg  
 625 630 635 640

Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro  
 645 650 655

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala  
 660 665 670

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His  
 675 680 685

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp  
 690 695 700

Ala Leu His Met Gln Ala Leu Pro Pro Arg  
 705 710

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<210> SEQ ID NO 345  
<211> LENGTH: 714  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 345

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

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

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

Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val  
50               55               60

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

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

Gly Gly Ser Gly Tyr Ala Leu His Asp Asp Tyr Tyr Gly Leu Asp Val  
100              105              110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser  
115              120              125

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr  
145              150              155              160

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

Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Gln Ser Ser Leu Lys  
180              185              190

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

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

Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln  
225              230              235              240

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly Gly  
245              250              255

Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Glu Ile Val Met  
260              265              270

Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr  
275              280              285

Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr  
290              295              300

Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr His Thr Ser  
305              310              315              320

Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly  
325              330              335

Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala  
340              345              350

Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gln  
355              360              365

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Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Ser Gln Ser Ala Leu  
 370 375 380

Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile  
 385 390 395 400

Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser  
 405 410 415

Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Asp  
 420 425 430

Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys  
 435 440 445

Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp  
 450 455 460

Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser Ser Thr Leu Tyr  
 465 470 475 480

Val Phe Gly Cys Gly Thr Lys Val Thr Val Leu Thr Thr Thr Pro Ala  
 485 490 495

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser  
 500 505 510

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr  
 515 520 525

Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala  
 530 535 540

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys  
 545 550 555 560

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met  
 565 570 575

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe  
 580 585 590

Pro Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg  
 595 600 605

Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn  
 610 615 620

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg  
 625 630 635 640

Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro  
 645 650 655

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala  
 660 665 670

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His  
 675 680 685

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp  
 690 695 700

Ala Leu His Met Gln Ala Leu Pro Pro Arg  
 705 710

<210> SEQ ID NO 346  
 <211> LENGTH: 714  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 346

Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln

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1	5	10	15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr			
20	25	30	
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu			
35	40	45	
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe			
50	55	60	
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu			
65	70	75	80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser			
85	90	95	
Ser Thr Leu Tyr Val Phe Gly Cys Gly Thr Lys Val Thr Val Leu Gly			
100	105	110	
Gly Gly Gly Ser Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser			
115	120	125	
Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp			
130	135	140	
Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro			
145	150	155	160
Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala			
165	170	175	
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser			
180	185	190	
Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn			
195	200	205	
Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly			
210	215	220	
Gly Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Ser Gly Gly			
225	230	235	240
Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys			
245	250	255	
Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu			
260	265	270	
Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu			
275	280	285	
Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Gln Ser			
290	295	300	
Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln			
305	310	315	320
Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr			
325	330	335	
Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Ser Tyr Ala Met Asp Tyr			
340	345	350	
Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser			
355	360	365	
Gln Val Gln Leu Gln Glu Ser Gly Gly Val Val Gln Pro Gly Arg			
370	375	380	
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr			
385	390	395	400
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Cys Leu Glu Trp Val			
405	410	415	
Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val			
420	425	430	

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Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr  
435 440 445

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
450 455 460

Gly Gly Ser Gly Tyr Ala Leu His Asp Asp Tyr Tyr Gly Leu Asp Val  
465 470 475 480

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Thr Thr Pro Ala  
485 490 495

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser  
500 505 510

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr  
515 520 525

Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala  
530 535 540

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys  
545 550 555 560

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met  
565 570 575

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe  
580 585 590

Pro Glu Glu Glu Gly Cys Glu Leu Arg Val Lys Phe Ser Arg  
595 600 605

Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn  
610 615 620

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg  
625 630 635 640

Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro  
645 650 655

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala  
660 665 670

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Gly Lys Gly His  
675 680 685

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp  
690 695 700

Ala Leu His Met Gln Ala Leu Pro Pro Arg  
705 710

<210> SEQ\_ID NO 347  
<211> LENGTH: 708  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 347

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr  
20 25 30

Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Cys Leu Glu Trp Ile  
35 40 45

Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Gln Ser Ser Leu Lys  
50 55 60

Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln Val Ser Leu

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65	70	75	80
Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala			
85	90	95	
Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln			
100	105	110	
Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser Asp Ile Gln			
115	120	125	
Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val			
130	135	140	
Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn Trp			
145	150	155	160
Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala			
165	170	175	
Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser			
180	185	190	
Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe			
195	200	205	
Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Leu Thr Phe Gly			
210	215	220	
Gln Gly Thr Lys Val Glu Ile Lys Gly Gly Gly Ser Gly Gly Gly			
225	230	235	240
Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Glu Val Gln Leu			
245	250	255	
Leu Glu Ser Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu			
260	265	270	
Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Ala Met Ser Trp			
275	280	285	
Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Ala Ile Ser			
290	295	300	
Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe			
305	310	315	320
Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn			
325	330	335	
Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Arg Glu			
340	345	350	
Trp Trp Gly Ser Trp Leu Phe Asp Tyr Trp Gly Gln Gly Thr Leu			
355	360	365	
Val Thr Val Ser Ser Gly Gly Gly Ser Glu Ile Val Met Thr Gln			
370	375	380	
Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser			
385	390	395	400
Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln			
405	410	415	
Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu			
420	425	430	
His Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp			
435	440	445	
Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr			
450	455	460	
Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr Phe Gly Cys Gly Thr			
465	470	475	480
Lys Leu Glu Ile Lys Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro			
485	490	495	

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Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys  
 500 505 510  
 Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala  
 515 520 525  
 Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu  
 530 535 540  
 Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys  
 545 550 555 560  
 Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr  
 565 570 575  
 Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Gly  
 580 585 590  
 Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala  
 595 600 605  
 Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg  
 610 615 620  
 Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu  
 625 630 635 640  
 Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn  
 645 650 655  
 Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met  
 660 665 670  
 Lys Gly Glu Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly  
 675 680 685  
 Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala  
 690 695 700  
 Leu Pro Pro Arg  
 705

<210> SEQ ID NO 348  
 <211> LENGTH: 708  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 348

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

Ser Ley Arg Ley Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr  
 20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Cys Ley Glu Trp Val  
 35 40 45

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

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Ley Tyr  
 65 70 75 80

Ley Gln Met Asn Ser Ley Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

Ala Arg Arg Glu Trp Trp Gly Glu Ser Trp Ley Phe Asp Tyr Trp Gly  
 100 105 110

Gln Gly Thr Ley Val Thr Val Ser Ser Gly Gly Ser Glu Ile  
 115 120 125

Val Met Thr Gln Ser Pro Ala Thr Ley Ser Ley Ser Pro Gly Glu Arg

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130	135	140
Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu Asn		
145	150	155
160		
Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr His		
165	170	175
Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly		
180	185	190
Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp		
195	200	205
Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr Phe		
210	215	220
Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Ser Gly Gly		
225	230	235
240		
Gly Gly Ser Gly Gly Ser Gly Gly Gly Ser Gln Val Gln		
245	250	255
Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr Leu Ser		
260	265	270
Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser		
275	280	285
Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly Val Ile		
290	295	300
Trp Gly Ser Glu Thr Thr Tyr Tyr Gln Ser Ser Leu Lys Ser Arg Val		
305	310	315
320		
Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys Leu Ser		
325	330	335
Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys His Tyr		
340	345	350
Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu		
355	360	365
Val Thr Val Ser Ser Gly Gly Ser Asp Ile Gln Met Thr Gln		
370	375	380
Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr		
385	390	395
400		
Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn Trp Tyr Gln Gln		
405	410	415
Lys Pro Gly Lys Ala Pro Lys Leu Ile Tyr Ala Ala Ser Ser Leu		
420	425	430
Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp		
435	440	445
Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr		
450	455	460
Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Leu Thr Phe Gly Cys Gly Thr		
465	470	475
480		
Lys Val Glu Ile Lys Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro		
485	490	495
Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys		
500	505	510
Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala		
515	520	525
Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu		
530	535	540
Lys Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys		
545	550	555
560		

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Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr  
 565 570 575  
 Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Gly  
 580 585 590  
 Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala  
 595 600 605  
 Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg  
 610 615 620  
 Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu  
 625 630 635 640  
 Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn  
 645 650 655  
 Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met  
 660 665 670  
 Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly  
 675 680 685  
 Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala  
 690 695 700  
 Leu Pro Pro Arg  
 705

<210> SEQ ID NO 349  
 <211> LENGTH: 486  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 349

Met Ala Leu Pro Val Thr Ala Leu Leu Pro Leu Ala Leu Leu Leu  
 1 5 10 15  
 His Ala Ala Arg Pro Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu  
 20 25 30  
 Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln  
 35 40 45  
 Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala  
 50 55 60  
 Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro  
 65 70 75 80  
 Ala Arg Phe Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile  
 85 90 95  
 Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly  
 100 105 110  
 Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys  
 115 120 125  
 Gly Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Ser Gln  
 130 135 140  
 Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr  
 145 150 155 160  
 Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly  
 165 170 175  
 Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly  
 180 185 190  
 Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Gln Ser Ser Leu Lys Ser

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195 200 205

Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys  
210 215 220

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

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly  
245 250 255

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

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

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

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

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

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

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

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

Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu  
385 390 395 400

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

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu  
420 425 430

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

Gly Met Lys Gly Glu Arg Arg Gly Lys Gly His Asp Gly Leu Tyr  
450 455 460

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

Gln Ala Leu Pro Pro Arg  
485

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<210> SEQ ID NO 350
<211> LENGTH: 465
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

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<400> SEQUENCE: 350

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

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

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile  
35 40 45

Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly  
50 55 60

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Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro  
 65 70 75 80  
 Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr  
 85 90 95  
 Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Ser  
 100 105 110  
 Gly Gly Gly Ser Gly Gly Ser Gln Val Gln Leu Gln Glu  
 115 120 125  
 Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys  
 130 135 140  
 Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg  
 145 150 155 160  
 Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly Val Ile Trp Gly Ser  
 165 170 175  
 Glu Thr Thr Tyr Tyr Gln Ser Ser Leu Lys Ser Arg Val Thr Ile Ser  
 180 185 190  
 Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr  
 195 200 205  
 Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly  
 210 215 220  
 Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val  
 225 230 235 240  
 Ser Ser Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr  
 245 250 255  
 Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala  
 260 265 270  
 Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile  
 275 280 285  
 Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser  
 290 295 300  
 Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr  
 305 310 315 320  
 Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu  
 325 330 335  
 Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Gly Cys Glu  
 340 345 350  
 Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln  
 355 360 365  
 Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu  
 370 375 380  
 Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly  
 385 390 395 400  
 Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln  
 405 410 415  
 Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu  
 420 425 430  
 Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr  
 435 440 445  
 Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro  
 450 455 460  
 Arg  
 465

-continued

<210> SEQ ID NO 351  
<211> LENGTH: 22  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 351

```
Met Leu Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro
1           5           10          15

Ala Phe Leu Leu Ile Pro
20
```

<210> SEQ ID NO 352  
<211> LENGTH: 66  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 352

```
atgcttctcc tggtgacaag ccttctgctc tgtgagttac cacaccaggc attcctcctg      60
atccca                                         66
```

<210> SEQ ID NO 353  
<211> LENGTH: 66  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 353

```
atgctgctgc tggtgaccag cctgctgctg tgcgagctgc cccaccccgc ctttctgctg      60
atcccc                                         66
```

<210> SEQ ID NO 354  
<211> LENGTH: 1461  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 354

```
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgtccca cgccgctcg      60
cccgaaattg ttagtaccca gtcacccgcc actcttagcc tttcacccgg tgagcgcgca    120
accctgtttt ggatggccctc ccaagacatc taaaatacc ttaattggta tcaacagaag    180
cccgacagg ctcctcgctt tctgtatctac cacaccaggc ggctccatc tggaatccct    240
gccaggttca ggggttgcgg atctgggacc gactacacc tcaactatcag ctcactgcag    300
ccagaggact tcgctgtcta tttctgtcag caagggaaaca ccctgcctta cacctttgga   360
caggggacca agtcgtcgat taaaggttga ggtggcagcg gaggaggtgg gtccggcggt   420
ggagggaaagcc aggttcaact ccaagaaagc ggaccgggtc ttgtgaagcc atcagaaact   480
cttctactga cttgtactgt gagcggagtg tctctccccc attacgggggt gtcttggatc   540
agacagaccac cggggaaaggg tctggaatgg attggagtga tttggggctc tgagactact  600
tactaccaat catccctcaa gtcacgcgtc accatctcaa aggacaactc taagaatcag   660
```

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725

726

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gtgtcactga aactgtcatc tggacccga gcccacaccg ccgtgtacta ttgcgctaa	720
cattactatt atggcgaggag ctacgcaatg gattactggg gacagggtac tctggtcacc	780
gtgtccagca ccactacccc agcacccgagg ccacccaccc cggctctac catgcctcc	840
cagcctctgt ccctgcttcc ggaggcatgt agacccgcag ctgggtgggc cgtgcataacc	900
cggggcttgc acttcgcctg cgatatctac atttgggccct ctctggctgg tacttgccgg	960
gtcctgtgc tttactcgt gatcaactt tactgtaaac ggggtggaa gaagctgtg	1020
tacatcttta agcaaccctt cataggcct gtgcagacta ctcaagagga ggacggctgt	1080
tcatgcccgt tcccagagga ggaggaaaggc ggctgcgaac tgccgtgaa attcagccgc	1140
agcgcagatg ctccagccta ccagcagggg cagaaccgcg tctacaacga actcaatctt	1200
ggtcggagag aggactacga cgtgtggac aacgggagag gacgggaccc agaaatggc	1260
ggaaagccgc gcagaaagaa tccccaaagag ggctgtaca acgagctcca aaaggataag	1320
atggcagaag cctatagcga gattggatg aaagggaaac gcagaagagg caaaggccac	1380
gacggactgt accaggact cagcacccgc accaaggaca cctatgacgc tcttcacatg	1440
caggccctgc cgcctcgta a	1461

&lt;210&gt; SEQ ID NO 355

&lt;211&gt; LENGTH: 1458

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 355

atggccctcc ctgtcaccgc cctgtgtctt ccgtgtggctc ttctgtccca cgccgctcg	60
cccgaaattt tgatgaccca gtcacccgc actcttagcc tttcacccgg tgagegcgc	120
accctgtctt gcagagcctc ccaagacatc taaaatacc ttaattggta tcaacagaag	180
cccgacagg ctccctcgctt tctgtatctac cacaccgcg ggctccatc tggaatccct	240
gccaggttca ggggttaggg atctgggacc gactacacc tcactatcag ctcactgcag	300
ccagaggact tcgctgtcta tttctgtcag caaggaaaca ccctgeccata cactttgga	360
cagggcacca agctcgagat taaagggtgg ggtggcagcg gaggagggtgg gtccggcggt	420
ggaggaagcc aggtccaact ccaagaaago ggaccgggtc ttgtgaagcc atcagaact	480
cttcactga ctgtactgt gacggagtg tctctccccc attacgggtt gtcttggatc	540
agacagccac cggggaaaggg tctggaatgg attggagtga tttggggctc tgagactact	600
tactaccat catccctcaa gtcacgcgtc accatctcaa aggacaactc taagaatcag	660
gtgtcactga aactgtcatc tggacccga gcccacaccg ccgtgtacta ttgcgctaa	720
cattactatt atggcgaggag ctacgcaatg gattactggg gacagggtac tctggtcacc	780
gtgtccagca ccactacccc agcacccgagg ccacccaccc cggctctac catgcctcc	840
cagcctctgt ccctgcttcc ggaggcatgt agacccgcag ctgggtgggc cgtgcataacc	900
cggggcttgc acttcgcctg cgatatctac atttgggccct ctctggctgg tacttgccgg	960
gtcctgtgc tttactcgt gatcaactt tactgtaaac ggggtggaa gaagctgtg	1020
tacatcttta agcaaccctt cataggcct gtgcagacta ctcaagagga ggacggctgt	1080
tcatgcccgt tcccagagga ggaggaaaggc ggctgcgaac tgccgtgaa attcagccgc	1140
agcgcagatg ctccagccta ccagcagggg cagaaccgcg tctacaacga actcaatctt	1200

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ggtcggagag aggagtacga cgtgctggac aagcggagag gacgggaccc agaaatggc	1260
ggaaagccgc gcagaaaagaa tccccaaagag ggctgtaca acgagctca aaaggataag	1320
atggcagaag octatagcga gattggtatg aaagggAAC gcagaagagg caaaggcac	1380
gacggactgt accagggact cagcacccgc accaaggaca cctatgacgc tttcacatg	1440
caggccctgc cgcctcg	1458

<210> SEQ ID NO 356  
<211> LENGTH: 1398  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 356

gaaatttgta tgacccagtc acccgccact cttagcctt cacccggta gcgcgcacc	60
ctgtcttgca gagcctccca agacatctca aaatacccta attggatca acagaagccc	120
ggacaggctc ctgccttct gatctaccac accagccggc tccattctgg aatccctgcc	180
aggttcagcg gtatcggtatc tgggaccgac tacaccctca ctatcagctc actgcagcca	240
gaggacttcg ctgtctatTT ctgtcagcaa gggAACACCC tgccctacac ctttggacag	300
ggcaccaagg tcgagattaa aggtggaggt ggcagcggag gaggtgggtc cggcggtgga	360
ggaagccagg tccaaCTCCA agaaAGCGGA ccgggtcttG tgaageccatc agaaactctt	420
tcactgactt gtactgtgag cggagtgtct ctcccccattt acgggggtgtc ttggatcaga	480
cagccaccgg ggaagggtct ggaatggatt ggagtgattt ggggctctga gactactac	540
taccaatcat ccctcaagtc acgcgtcacc atctcaaagg acaactctaa gaatcaggt	600
tcactgaaac tgcgtatctgt gacccgcagec gacaccgcgc tgtaactattt cgctaagcat	660
tactattatg cggggagcta cgcaatggat tactggggac agggtactct ggtcaccgt	720
tccagcacca ctaccccaaggc accgaggccca cccaccccccgttccatccat cgcctccag	780
cctctgtccc tgcgtccggaa ggcatgtaga cccgcagctg gtggggccgt gcatacccg	840
ggtcttgcact tgcctgcga tatctacatt tggcccccctc tggctggtaC ttgcgggtc	900
ctgctgtttt cactcgatgactt cactcttac tgtaagecgcg gtcggaaagaa gctgtgtac	960
atctttaaagc aacccttcat gaggctgtg cagactactc aagaggagga cggctgtca	1020
tgcgggttcc cagaggagga ggaaggccgc tgcgaactgc gcgtgaaatt cagccgcagc	1080
gcagatgttc cagcctacca gcagggccag aaccagctct acaacgaact caatcttgc	1140
cgagagagg agtacgacgt gctggacaag cggagaggac gggaccaga aatggccgg	1200
aagccgcgcga gaaagaatcc ccaagaggcc ctgtacaacg agctccaaa ggataagatg	1260
gcagaaggctt atagcgagat tggatgaaa gggaaacgcga gaagaggccaa aggccacgc	1320
ggactgtacc agggactcag caccgcacc aaggacacct atgacgctct tcacatgcag	1380
gcctgcgcgc ctcggtaa	1398

<210> SEQ ID NO 357  
<211> LENGTH: 360  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 357

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```
caggtccagc tgcaggaatc aggaccaggg ctggtgaaac ctagcgaaac tctgagtctg      60
acttgtaccc ttcctgggggt gtctctgcca gactacggcg tgagctggat cagacagccc     120
cctggcaagt gcctggagtg gatcggcggt atctggggct ccgagaccac atactatcat     180
agctccctga agtctcggtt gaccatctcc aaggacaact ctaagaatca ggtgagcctg     240
aagctgtcta gcgtgaccgc cgccgataca gccgtgtact attgtgccaa gcactactat     300
tacggcggct cctatgccc ggattactgg ggccaggggca ccctggtgac agtgtccctt     360
```

<210> SEQ ID NO 358  
<211> LENGTH: 360  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 358

```
caggtccagc tgcaggaatc cggcccagga ctggtgaaagc ctagcgagac cctgtccctg      60
acctgcacag tgagcggcggt gtccctgccc gattacggcg tgagctggat cagacagccc     120
cctggcaagt gtctggagtg gateggcggt atctggggct ctgagaccac atactatcat     180
tcctctctga agagcagggt gaccatctct aaggacaaca gcaagaatca ggtgtccctg     240
aagctgagct ccgtgaccgc agcagataca gccgtgtact attgcgccaa gcactactat     300
tacggcggct cctatgctat ggattattgg ggccaggggca ctctggtcac tgtctcatca     360
```

<210> SEQ ID NO 359  
<211> LENGTH: 360  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 359

```
caggtgcagc tgcaggaatc tggaccggta ctggtgaaac ctagtgaac tctgtctctg      60
acttgtaccc ttcctgggggt ctcactgcca gactacggcg tgcctggat cagacagccc     120
cctggcaagt gcctggagtg gateggcggt atctggggct ctgagaccac atactatcat     180
agctccctga agagcgggtt gaccatctcc aaggacaact ctaagaatca ggtgtccctg     240
aagctgtcta gcgtgaccgc cgccgataca gccgtgtact attgtgccaa gcactactat     300
tacggcggca gctatgccc ggattactgg ggccaggggca ccctggtgac agtgtccctt     360
```

<210> SEQ ID NO 360  
<211> LENGTH: 360  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 360

```
caggtccagc tgcaggaag cggcccagga ctggtgaaagc ctagcgagac cctgtccctg      60
acctgcacag tgagcggcggt gtccctgccc gattacggcg tgcctggat cagacagccc     120
cctggcaagt gtctggagtg gateggcggt atctggggct ccgagaccac atactatcat     180
tcctctctga agtcttaggggt gacaatctct aaggacaaca gcaagaatca ggtgagcctg     240
aagctgagct ccgtgaccgc agcagataca gccgtgtact attgtgccaa gcactactat     300
```

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```
tacggcggct cttatgctat ggattattgg gggcagggca ctctggtcac tgtctcaagc      360
```

```
<210> SEQ ID NO 361
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polynucleotide
```

```
<400> SEQUENCE: 361
```

```
caggtgcagc tgcaggagag cggcccgagga ctgggtgaagc cttccgagac actgtctctg      60
acctgtacag tgagcggcgt gtccctgccc gactacggcg tgtcctggat cagacagcca      120
cctggcaagg gactggagtg gateggcgtg atctggggca gcgagaccac atactatcat      180
agctccctga agtccagggt gaccatcago aaggacaact ccaagaatca ggtgagctg      240
aagctgtcta gcgtgaccgc cgccgataca gccgtgtact attgcgccaa gcactactat      300
tacggcggct cctatgccat ggattactgg ggccagggca ccctggtcac agtgtccct      360
```

```
<210> SEQ ID NO 362
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polynucleotide
```

```
<400> SEQUENCE: 362
```

```
caggtgcagc tgcaggagtc tggcccgagga ctgggtgaagc cttctgagac cctgagcctg      60
acctgcacag tgccggcgt gtctctgccc gattacggcg tgtcctggat cagacagcca      120
cctggcaagg gactggagtg gateggcgtg atctggggct ctgagaccac atactatcat      180
tctagcctga agagccgggt gacaatctcc aaggacaact ctaagaatca ggtgtccctg      240
aagctgtctt ctgtgaccgc cgccgataca gccgtgtact attgtgccaa gcactactat      300
tacggcggca gctatgccat ggactactgg ggccagggca ccctggtgac agtgagctcc      360
```

```
<210> SEQ ID NO 363
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polynucleotide
```

```
<400> SEQUENCE: 363
```

```
caggtgcagc tgcaggagtc tggcccgagga ctgggtgaagc cttctgagac cctgagcctg      60
acctgcacag tgagcggcgt gtccctgccc gattacggcg tgtcctggat cagacagcca      120
cctggcaagg gactggagtg gateggcgtg atctggggca gcgagaccac atactatcat      180
tctctctga agtccagggt gacaatctcc aaggacaact ctaagaatca ggtgagctg      240
aagctgagct ccgtgaccgc agcagataca gccgtgtact attgcgccaa gcactactat      300
tacggcggct cctatgccat ggactactgg ggccagggca ccctggtcac agtgtcttagc      360
```

```
<210> SEQ ID NO 364
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
```

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## polynucleotide

&lt;400&gt; SEQUENCE: 364

caggtgcagc	tgccaggagtc	cgccccagga	ctggtaagc	cttccgagac	actgtctctg	60
acctgtacag	tgtccggcgt	gtctctgcc	gactacggcg	tgagctggat	cagacagcca	120
cctggcaagg	gactggagt	gatccggcgt	atctggggct	ctgagaccac	atactatcg	180
tcctctctga	agagccgggt	gaccatcago	aaggacaact	ccaagaatca	ggtgtccctg	240
aagctgagct	ccgtgaccgc	agcagataca	gccgtgtact	attgcgccaa	gcactactat	300
tacggcggca	gctatgccat	ggattactgg	ggccaggggca	ccctggtgac	agtgtctagc	360

&lt;210&gt; SEQ ID NO 365

&lt;211&gt; LENGTH: 321

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 365

gagatcgtga	tgacccagag	cccagccaca	ctgagcctgt	ccccaggaga	gagggccaca	60
ctgtcttgta	gagccagcca	ggatatctcc	aagtatctga	actggcacca	gcagaaggct	120
ggacaggcac	caaggctgct	gatctaccac	acctcttagac	tgcacagcgg	catccctgcc	180
aggttttctg	gcagcggctc	cggcacagac	tataccctga	caatctctag	cctgcagcca	240
gaggatttcg	ccgtgtactt	ttgtcagcag	ggcaataactc	tgccatacac	ctttggatgc	300
ggaactaaac	tggaaatcaa	g				321

&lt;210&gt; SEQ ID NO 366

&lt;211&gt; LENGTH: 321

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 366

gaaatttgta	tgacccagtc	ccccgtact	ctgtctctgt	ccccggaga	acgggctact	60
ctgtcttgta	gcgcctccca	ggatattagc	aagtacctga	actggtatca	gcagaaggca	120
ggacaggcac	caaggctgct	gatctaccac	acctctcgcc	tgcacagcgg	catccctgca	180
cggttctctg	gcagcggctc	cggcacagac	tacaccctga	caatcagctc	cctgcagcc	240
gaggatttcg	ccgtgtactt	ttgccagcag	ggcaataacc	tgccataatac	atttggctgt	300
ggcaccaagc	tggagatcaa	g				321

&lt;210&gt; SEQ ID NO 367

&lt;211&gt; LENGTH: 321

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 367

gagatcgtga	tgacccagtc	cccagccaca	ctgagcctgt	ccccaggaga	gagggccacc	60
ctgtcttgta	gagccagcca	ggatatctcc	aagtatctga	actggcacca	gcagaaggct	120
ggacaggcac	caaggctgct	gatctaccac	acctctagac	tgcacagcgg	catccctgcc	180

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aggaaaaatccg	gcagcggctc	cggcacagac	tataccctga	caatctctag	cctgcagcca	240
gaggatttcg	ccgtgtactt	ttgtcagcag	ggaaataactc	tgccatacac	cttggatgc	300
ggaccaaggc	ttggatccaa	ttggatccaa	ttggatccaa	ttggatccaa	ttggatccaa	321

<210> SEQ ID NO 368  
<211> LENGTH: 321  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 368

gagattgtga	tgaccaggc	ccccggccacc	ctgagttctga	gccccggaga	acggatcacc	60
ctgagttgcc	gagcttccca	ggacatccc	aagtaccc	actggatcc	gcagaaggca	120
ggacaggcac	caaggctgct	gatctaccac	acccctcgcc	tgcacagcgg	catcccgca	180
cggttctctg	gcagcggctc	cggcacagac	tacaccctga	caatcagctc	cctgcagcct	240
gaggatttcg	ccgtgtactt	ttgtcagcag	ggcaataccc	tgccatatac	atttggctgt	300
ggaccaaggc	ttggatccaa	ttggatccaa	ttggatccaa	ttggatccaa	ttggatccaa	321

<210> SEQ ID NO 369  
<211> LENGTH: 321  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 369

gagatcgtga	tgaccaggc	tccagccaca	ctgtctctga	gcccaggaga	gagggccacc	60
ctgtcttgcc	gcccaggcca	ggatatctcc	aagtatctga	actggatcca	gcagaaggca	120
ggacaggcac	caaggctgct	gatctaccac	acccctcgcc	tgcacagcgg	catcccgca	180
cggttctccg	gctctggcag	cggcacagac	tacaccctga	caatctccctc	tctgcagccc	240
gaggatttcg	ccgtgtatcc	ttgtcagcag	ggcaataccc	tgccatatac	atttggccag	300
ggaccaaggc	ttggatccaa	ttggatccaa	ttggatccaa	ttggatccaa	ttggatccaa	321

<210> SEQ ID NO 370  
<211> LENGTH: 321  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 370

gagatcgtga	tgaccaggag	ccccggccaca	ctgagcctgt	ccccaggaga	gagggccacc	60
ctgagctgca	gagcctccca	ggatatctct	aagtatctga	actggatcca	gcagaaggct	120
ggacaggcac	caaggctgct	gatctaccac	accaggcagac	tgcactccgg	catccctgca	180
cggttctctg	gcagcggctc	cggcacagac	tacaccctga	caatctctag	cctgcagcct	240
gaggatttcg	ccgtgtatcc	ttgtcagcag	ggcaataccc	tgccatatac	atttggccag	300
ggaccaaggc	ttggatccaa	ttggatccaa	ttggatccaa	ttggatccaa	ttggatccaa	321

<210> SEQ ID NO 371  
<211> LENGTH: 321  
<212> TYPE: DNA

737

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-continued

<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 371

gagatctgtga tgacccagag cccagccaca ctgtctgtca gcccaggaga gagggccacc	60
ctgagactgtc ggcgcctccca ggatatctct aagtatctga actggatcca gcagaagcca	120
ggacaggcac caaggctgtct gatctaccac accagccgcc tgcactccgg catcccgac	180
cggttctccg gctctggcag cggcacagac tacaccctga caatctccctc tctgcagccc	240
gaggatttcg ccgtgttattt ttgccagcag ggcaataccac tgccttacac atttggccag	300
ggcaccaaaqc tqqagatcaa q	321

<210> SEQ ID NO 372

<211> LENGTH: 321

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER IN

### polynucleotide

<400> SEQUENCE: 372

gagatcgtga tgacccagtc tccagccaca ctgagcctgt cccccaggaga gagggccacc	60
ctgtcttgcg gagccagcca ggatatctcc aagtatctga actggtagcca gcagaagct	120
ggacaggcac caaggctgct gatctaccac acctctagac tgcacagccg catcccgca	180
aggttctctg gcagcggctc cggcacagac tacaccctga caatctctag cctgcagccct	240
gaggatttcg ccgtgtatTT tgccagcag ggcaatacccg tgccatacac atttggccag	300
ggcaccaagc tggagatcaa g	321

<210> SEQ ID NO 373

<211> LENGTH: 242

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 373

1                   5                   10                   15  
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile  
35 40 45

Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly  
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro  
65 70 75 80

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr  
85 90 95

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

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

Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys  
130 135 140

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Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg  
145                150                155                160

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

Glu Thr Thr Tyr Tyr Ser Ser Ser Leu Lys Ser Arg Val Thr Ile Ser  
180                185                190

Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr  
195                200                205

Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly  
210                215                220

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

Ser Ser

<210> SEQ ID NO 374

<211> LENGTH: 242

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 374

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr  
20                25                30

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

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

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

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala  
85                90                95

Lys His Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln  
100                105                110

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly Gly  
115                120                125

Gly Ser Gly Gly Gly Ser Glu Ile Val Met Thr Gln Ser Pro Ala  
130                135                140

Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala  
145                150                155                160

Ser Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly  
165                170                175

Gln Ala Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly  
180                185                190

Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu  
195                200                205

Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln  
210                215                220

Gln Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu  
225                230                235                240

Ile Lys

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<210> SEQ ID NO 375  
<211> LENGTH: 242  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 375

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

Thr	Leu	Ser	Leu	Thr	Cys	Thr	Val	Ser	Gly	Val	Ser	Leu	Pro	Asp	Tyr
				20			25				30				

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

Gly	Val	Ile	Trp	Gly	Ser	Glu	Thr	Thr	Tyr	Tyr	Gln	Ser	Ser	Leu	Lys
				50			55		60						

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

Lys	Leu	Ser	Ser	Val	Thr	Ala	Ala	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	Ala
				85			90				95				

Lys	His	Tyr	Tyr	Gly	Gly	Ser	Tyr	Ala	Met	Asp	Tyr	Trp	Gly	Gln
				100			105			110				

Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	Ser	Gly	Gly	Gly
				115			120		125					

Gly	Ser	Gly	Gly	Gly	Ser	Glu	Ile	Val	Met	Thr	Gln	Ser	Pro	Ala
				130			135		140					

Thr	Leu	Ser	Leu	Ser	Pro	Gly	Glu	Arg	Ala	Thr	Leu	Ser	Cys	Arg	Ala
145				150			155		160						

Ser	Gln	Asp	Ile	Ser	Lys	Tyr	Leu	Asn	Trp	Tyr	Gln	Gln	Lys	Pro	Gly
				165			170		175						

Gln	Ala	Pro	Arg	Leu	Leu	Ile	Tyr	His	Thr	Ser	Arg	Leu	His	Ser	Gly
				180			185		190						

Ile	Pro	Ala	Arg	Phe	Ser	Gly	Ser	Gly	Thr	Asp	Tyr	Tyr	Thr	Leu
				195			200		205					

Thr	Ile	Ser	Ser	Leu	Gln	Pro	Glu	Asp	Phe	Ala	Val	Tyr	Phe	Cys	Gln
				210			215		220						

Gln	Gly	Asn	Thr	Leu	Pro	Tyr	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu
				225			230		235			240			

Ile Lys

<210> SEQ ID NO 376  
<211> LENGTH: 247  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 376

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

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

Leu	Asn	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Leu	Leu	Ile
				35			40		45						

Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly

-continued

50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro  
 65 70 75 80

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr  
 85 90 95

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

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

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

Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly  
 145 150 155 160

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

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Ser Ser Ser Leu Lys Ser  
 180 185 190

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

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

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly  
 225 230 235 240

Thr Leu Val Thr Val Ser Ser  
 245

&lt;210&gt; SEQ ID NO 377

&lt;211&gt; LENGTH: 247

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 377

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

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

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile  
 35 40 45

Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly  
 50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro  
 65 70 75 80

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr  
 85 90 95

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

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

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

Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly  
 145 150 155 160

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

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Gln Ser Ser Leu Lys Ser  
180 185 190

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

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

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly  
225 230 235 240

Thr Leu Val Thr Val Ser Ser  
245

<210> SEQ ID NO 378

<211> LENGTH: 247

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 378

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr  
20 25 30

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

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

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

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala  
85 90 95

Lys His Tyr Tyr Tyr Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln  
100 105 110

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly Gly  
115 120 125

Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Glu Ile Val Met  
130 135 140

Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr  
145 150 155 160

Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr  
165 170 175

Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr His Thr Ser  
180 185 190

Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly  
195 200 205

Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala  
210 215 220

Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gln  
225 230 235 240

Gly Thr Lys Leu Glu Ile Lys  
245

<210> SEQ ID NO 379

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<211> LENGTH: 247
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide
```

<400> SEQUENCE: 379

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr  
20 25 30

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

Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Gln Ser Ser Leu Lys  
                   50                  55                  60

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

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Tyr Cys Ala  
85 90 95

Lys His Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln  
161 162 163 164 165 166 167 168

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly

Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Met  
130 135 140

Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr  
145 150 155 160

Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr  
165 170 175

Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr His Thr Ser  
180 185 190

Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly

Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala  
210 215 220

Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gln  
225 230 235 240

245

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<210> SEQ ID NO 380
<211> LENGTH: 247
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide
```

<400> SEQUENCE: 380

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

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

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile  
35 40 45

Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly  
50 55 60

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Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro  
65 70 75 80

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr  
85 90 95

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

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

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

Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly  
145 150 155 160

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

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

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

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

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly  
225 230 235 240

Thr Leu Val Thr Val Ser Ser  
245

<210> SEQ ID NO 381  
<211> LENGTH: 247  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 381

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr  
20 25 30

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

Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ser Leu Lys  
50 55 60

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

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala  
85 90 95

Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln  
100 105 110

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly Gly  
115 120 125

Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Glu Ile Val Met  
130 135 140

Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr  
145 150 155 160

Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr

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165	170	175
Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr His Thr Ser		
180	185	190
Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly		
195	200	205
Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala		
210	215	220
Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gln		
225	230	235
Gly Thr Lys Leu Glu Ile Lys		
245		

<210> SEQ ID NO 382  
<211> LENGTH: 242  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 382

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly		
1	5	10
		15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr		
20	25	30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile		
35	40	45
Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly		
50	55	60
Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro		
65	70	75
		80
Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr		
85	90	95
Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Ser		
100	105	110
Gly Gly Gly Ser Gly Gly Ser Gln Val Gln Leu Gln Glu		
115	120	125
Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys		
130	135	140
Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg		
145	150	155
		160
Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly Val Ile Trp Gly Ser		
165	170	175
Glu Thr Thr Tyr Tyr Asn Ser Ser Leu Lys Ser Arg Val Thr Ile Ser		
180	185	190
Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr		
195	200	205
Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly		
210	215	220
Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val		
225	230	235
		240
Ser Ser		

<210> SEQ ID NO 383  
<211> LENGTH: 242  
<212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 383

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

Thr	Leu	Ser	Leu	Thr	Cys	Thr	Val	Ser	Gly	Val	Ser	Leu	Pro	Asp	Tyr
				20			25				30				

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

Gly	Val	Ile	Trp	Gly	Ser	Glu	Thr	Thr	Tyr	Tyr	Asn	Ser	Ser	Leu	Lys
				50			55		60						

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

Lys	Leu	Ser	Ser	Val	Thr	Ala	Ala	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	Ala
				85			90			95					

Lys	His	Tyr	Tyr	Gly	Gly	Ser	Tyr	Ala	Met	Asp	Tyr	Trp	Gly	Gln
				100			105			110				

Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	Ser	Gly	Gly	Gly
				115			120		125					

Gly	Ser	Gly	Gly	Gly	Ser	Glu	Ile	Val	Met	Thr	Gln	Ser	Pro	Ala
				130			135		140					

Thr	Leu	Ser	Leu	Ser	Pro	Gly	Glu	Arg	Ala	Thr	Leu	Ser	Cys	Arg	Ala
145					150			155			160				

Ser	Gln	Asp	Ile	Ser	Lys	Tyr	Leu	Asn	Trp	Tyr	Gln	Gln	Lys	Pro	Gly
				165			170			175					

Gln	Ala	Pro	Arg	Leu	Leu	Ile	Tyr	His	Thr	Ser	Arg	Leu	His	Ser	Gly
				180			185			190					

Ile	Pro	Ala	Arg	Phe	Ser	Gly	Ser	Gly	Thr	Asp	Tyr	Trp	Tyr	Thr	Leu
				195			200			205					

Thr	Ile	Ser	Ser	Leu	Gln	Pro	Glu	Asp	Phe	Ala	Val	Tyr	Phe	Cys	Gln
				210			215			220					

Gln	Gly	Asn	Thr	Leu	Pro	Tyr	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu
				225			230			235			240		

Ile Lys

<210> SEQ ID NO 384  
<211> LENGTH: 1467  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 384

atgcttcgtcc	tggtgacaag	ccttctgctc	tgtgagttac	cacaccgc	attccctctg	60
atccccagaca	tccagatgac	acagactaca	tcctccctgt	ctgcctct	gggagacaga	120
gttcaccatca	gttgcgggc	aagtcaaggac	attagtaaat	atttaaat	gtatcagcag	180
aaaccagatg	gaactgttaa	actccgtac	taccatacat	caagattaca	ctcaggagtc	240
ccatcaagat	tcaatggcag	tgggtctgga	acagattatt	ctctcaccat	tagcaacactg	300
gagcaagaag	atattgccac	ttactttgc	caacagggtta	atacgcttcc	gtacacgttc	360
ggggggggga	ctaagttgga	aataaacaggc	tccacctctg	gatccggcaa	gcccgatct	420

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ggcgagggat ccaccaaggg cgaggtgaaa ctgcaggagt caggacctgg cctggtggcg    480
ccctcacaga gcctgtccgt cacatgcact gtctcagggg tctcattacc cgactatggt    540
gtaagctgga ttccgcagcc tccacgaaag ggtctggagt ggctgggagt aatatgggt    600
agtgaaacca catactataa ttcaagtcctc aaatccagac tgaccatcat caaggacaac    660
tccaagagcc aagttttctt aaaaatgaac agtctgcaaa ctgatgacac agccattac    720
tactgtccca aacattatta ctacgggtgt agctatgcta tggactactg gggtaagga    780
acctcagtca ccgtctccctc agcggccgca attgaagtt tgcatactcc tccttaccta    840
gacaatgaga agagcaatgg aaccattatc catgtgaaag ggaaacacct ttgtccaagt    900
cccctatttc ccggaccccttc taagcccttt tgggtgctgg tgggtgggttgg gggagtctg    960
gcttgctata gcttgctgt aacagtggcc ttattattt tctgggtgag gagtaagagg    1020
agcaggctcc tgcacagtga ctacatgaac atgactcccc gcccggccg gcccacccgc    1080
aagcattacc agccctatgc cccaccacgc gacttcgcag cctategcctc cagagtgaag    1140
ttcagcagga ggcgcagacgc cccgcgtac cagcaggccg agaaccagct ctataacgag    1200
ctcaatctag gacgaagaga ggagtagcgt gtttggaca agagacgtgg ccgggacccct    1260
gagatggggg gaaagccgag aaggaagaac cctcaggaag gcctgtacaa tgaactgcag    1320
aaagataaga tggcgaggc ctacagttagt attggatgaa aaggcgagcg ccggaggggc    1380
aaggggcacg atggccctta ccagggtctc agtacagcca ccaaggacac ctacgacgcc    1440
tttcacatgc aggccctgcc ccctcgc                                         1467

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&lt;210&gt; SEQ ID NO 385

&lt;211&gt; LENGTH: 489

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 385

Met	Leu	Leu	Leu	Val	Thr	Ser	Leu	Leu	Leu	Cys	Glu	Leu	Pro	His	Pro
1				5			10			15					

Ala	Phe	Leu	Leu	Ile	Pro	Asp	Ile	Gln	Met	Thr	Gln	Thr	Thr	Ser	Ser
				20			25		30						

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

Gln	Asp	Ile	Ser	Lys	Tyr	Leu	Asn	Trp	Tyr	Gln	Gln	Lys	Pro	Asp	Gly
				50		55		60							

Thr	Val	Lys	Leu	Leu	Ile	Tyr	His	Thr	Ser	Arg	Leu	His	Ser	Gly	Val
65					70		75		80						

Pro	Ser	Arg	Phe	Ser	Gly	Ser	Gly	Thr	Asp	Tyr	Ser	Leu	Thr		
					85		90		95						

Ile	Ser	Asn	Leu	Glu	Gln	Glu	Asp	Ile	Ala	Thr	Tyr	Phe	Cys	Gln	Gln
				100		105			110						

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

Thr	Gly	Ser	Thr	Ser	Gly	Ser	Gly	Lys	Pro	Gly	Ser	Gly	Glu	Gly	Ser
130				135		140									

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

Pro	Ser	Gln	Ser	Leu	Ser	Val	Thr	Cys	Thr	Val	Ser	Gly	Val	Ser	Leu
				165		170		175							

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Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu  
 180 185 190

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

Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln  
 210 215 220

Val Phe Leu Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr  
 225 230 235 240

Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr  
 245 250 255

Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ala Ala Ile Glu  
 260 265 270

Val Met Tyr Pro Pro Pro Tyr Leu Asp Asn Glu Lys Ser Asn Gly Thr  
 275 280 285

Ile Ile His Val Lys Gly Lys His Leu Cys Pro Ser Pro Leu Phe Pro  
 290 295 300

Gly Pro Ser Lys Pro Phe Trp Val Leu Val Val Val Gly Gly Val Leu  
 305 310 315 320

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

Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr  
 340 345 350

Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro  
 355 360 365

Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Val Lys Phe Ser Arg Ser  
 370 375 380

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

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

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

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

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

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

Leu His Met Gln Ala Leu Pro Pro Arg  
 485

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<210> SEQ ID NO 386  
<211> LENGTH: 801  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 386

atgcttctcc	tggtgacaag	ccttctgctc	tgtgagttac	cacaccgc	attcctcctg	60
atccccagaca	tccatgatgc	acagactaca	tcctccctgt	ctgcctctct	gggagacaga	120
gtcaccatca	gttgcaggc	aagtcaaggac	attagtaaat	atttaaatg	gtatcagcag	180
aaaccagatg	gaactgttaa	actcctgatc	taccatacat	caagattaca	ctcaggagtc	240

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ccatcaaggt tcagtggcag tgggtctgga acagattatt ctctcaccat tagcaacctg	300
gagcaagaag atattgccac ttactttgc caacaggta atacgcttc gtacacgttc	360
ggagggggga ctaagttgga aataacaggo tccacctctg gatccggcaa gcccggatct	420
ggcgagggat ccaccaaggg cgaggtgaaa ctgcaggagt caggacctgg cctggtggcg	480
ccctcacaga gcctgtccgt cacatgcact gtctcagggg ttcattacc cgactatgg	540
gtaagctgga ttgcgcagcc tccacgaaag ggtctggagt ggctggagt aatatgggt	600
agtgaaacca catactataa ttcaagctctc aaatccagac tgaccatcat caaggacaac	660
tccaagagcc aagtttctt aaaaatgaac agtctgcaaa ctgatgacac agccattac	720
tactgtgcca aacattatta ctacggtggt agctatgcta tggactactg gggtaagga	780
acctcagtca cctgtccctc a	801

<210> SEQ ID NO 387  
<211> LENGTH: 266  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 387

Met Leu Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro			
1	5	10	15

Ala Phe Leu Leu Ile Pro Asp Ile Gln Met Thr Gln Thr Thr Ser Ser			
20	25	30	

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

Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly			
50	55	60	

Thr Val Lys Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Val			
65	70	75	80

Pro Ser Arg Phe Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr			
85	90	95	

Ile Ser Asn Leu Glu Gln Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln			
100	105	110	

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

Thr Gly Ser Thr Ser Gly Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser			
130	135	140	

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

Pro Ser Gln Ser Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu			
165	170	175	

Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu			
180	185	190	

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

Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln			
210	215	220	

Val Phe Leu Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr			
225	230	235	240

Tyr Cys Ala Lys His Tyr Tyr Gly Ser Tyr Ala Met Asp Tyr			
245	250	255	

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Trp Gly Gln Gly Thr Ser Val Thr Val Ser  
260                    265

<210> SEQ ID NO 388  
<211> LENGTH: 1401  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 388

gacatccaga	tgacacagac	tacatcctcc	ctgtctgcct	ctctgggaga	cagagtccacc	60
atcagttgca	ggccaagtca	ggacattagt	aaatatttaa	attggtatca	gcagaaaacca	120
gatggaaactg	ttaaactcct	gatctaccat	acatcaagat	tacactcagg	agtcccatca	180
aggttcagtg	gcagtgggtc	tggaacagat	tattctctca	ccattagcaa	cctggagcaa	240
gaagatattg	ccacttactt	ttgccaacag	ggtataacgc	ttccgtacac	gttcggaggg	300
gggactaagt	tggaaataac	aggctccaco	tctggatecg	gcaagccccgg	atctggcgag	360
ggatccacca	agggcgaggt	gaaactgcag	gagtcaggac	ctggcctgg	ggcgcacctca	420
cagagcctgt	cogtcacatg	cactgtctca	ggggtctcat	tacccgacta	tggtgtaagc	480
tggatcgcc	agcctccacg	aaagggtctg	gagtggctgg	gagtaatatg	ggtagtgaa	540
accacatact	ataattcage	tctcaaatec	agactgacca	tcatcaagga	caactccaag	600
agccaagttt	tctaaaaat	gaacagtctg	caaactgtat	acacagccat	ttactactgt	660
gccaaacatt	attactacgg	tggtagctat	gctatggact	actggggtca	aggaacctca	720
gtcaccgtct	cctcagcggc	cgcaattgaa	gttatgtatc	ctccctccta	cctagacaat	780
gagaagagca	atggaaccat	tatccatgtg	aaaggaaac	acctttgtcc	aagtccccta	840
ttccccggac	cttctaagcc	ctttgggtg	ctgggtgg	ttggggggagt	cctggctgc	900
tatagctgc	tagtaacagt	ggcctttatt	attttctgg	tgaggagtaa	gaggagcagg	960
ctcctgcaca	gtgactacat	gaacatgact	ccccggccgc	ccgggeccac	ccgcaagcat	1020
taccageccct	atgccccacc	acgegacttc	gcagcctatc	gctccagagt	gaagttcagc	1080
aggagcgcag	acgccccgc	gtaccagcag	ggccagaacc	agctctataa	cgagctcaat	1140
ctaggacgaa	gagaggagta	cgatgtttg	gacaagagac	gtggcgggga	ccctgagatg	1200
gggggaaagc	cgagaaggaa	gaaccctcag	gaaggcctgt	acaatgaact	gcagaaagat	1260
aagatggcgg	aggcctacag	tgagattggg	atgaaaggcg	agcgccggag	gggcaagggg	1320
cacgatggcc	tttaccaggg	tctcagtaa	gccaccaagg	acacctacga	cgccttcac	1380
atgcaggccc	tgccccctcg	c				1401

<210> SEQ ID NO 389  
<211> LENGTH: 467  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 389

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

Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr		
20	25	30

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Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile  
   35               40               45  
 Tyr His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly  
   50               55               60  
 Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln  
   65               70               75               80  
 Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr  
   85               90               95  
 Thr Phe Gly Gly Thr Lys Leu Glu Ile Thr Gly Ser Thr Ser Gly  
   100              105              110  
 Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser Thr Lys Gly Glu Val Lys  
   115              120              125  
 Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser  
   130              135              140  
 Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser  
   145              150              155              160  
 Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile  
   165              170              175  
 Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu  
   180              185              190  
 Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn  
   195              200              205  
 Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr  
   210              215              220  
 Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser  
   225              230              235              240  
 Val Thr Val Ser Ser Ala Ala Ala Ile Glu Val Met Tyr Pro Pro Pro  
   245              250              255  
 Tyr Leu Asp Asn Glu Lys Ser Asn Gly Thr Ile Ile His Val Lys Gly  
   260              265              270  
 Lys His Leu Cys Pro Ser Pro Leu Phe Pro Gly Pro Ser Lys Pro Phe  
   275              280              285  
 Trp Val Leu Val Val Val Gly Val Leu Ala Cys Tyr Ser Leu Leu  
   290              295              300  
 Val Thr Val Ala Phe Ile Ile Phe Trp Val Arg Ser Lys Arg Ser Arg  
   305              310              315              320  
 Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly Pro  
   325              330              335  
 Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala  
   340              345              350  
 Tyr Arg Ser Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr  
   355              360              365  
 Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg  
   370              375              380  
 Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met  
   385              390              395              400  
 Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu  
   405              410              415  
 Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys  
   420              425              430  
 Gly Glu Arg Arg Arg Gly Lys His Asp Gly Leu Tyr Gln Gly Leu  
   435              440              445

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Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu  
 450                    455                    460

Pro Pro Arg  
 465

<210> SEQ ID NO 390  
 <211> LENGTH: 735  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 390

gacatccaga	tgacacagac	tacatccctcc	ctgtctgcct	ctctgggaga	cagagtccacc	60
atcagttgca	gggcaagtca	ggacattagt	aaatatttaa	attggtatca	gcagaaacca	120
gatggaactg	ttaaactcct	gatctaccat	acatcaagat	tacactcagg	agtcccatca	180
aggttcagtg	gcagtgggtc	tggyaacat	tattctctca	ccattagcaa	cctggagcaa	240
gaagatattg	ccacttactt	ttgccaacag	ggtaatacgc	ttccgtacac	gttcggaggg	300
gggactaagt	tggaaaataac	aggctccacc	tctggatcccg	gcaagccccgg	atctggcgag	360
ggatccacca	aggggcgaggt	gaaactgcag	gagtcaggac	ctggcctgg	ggccccccta	420
cagagcctgt	ccgtcacatg	cactgtctca	ggggctctcat	tacccgacta	tggtgtaagc	480
tggattecgc	agcctccacg	aaagggtctg	gagttggctgg	gagtaatatg	ggtagtgaa	540
accacacata	ataattcagc	tctcaaattcc	agactgacca	tcatcaagga	caactccaaag	600
agccaaagttt	tctaaaaat	gaacagtctg	caaactgatg	acacagccat	ttactactgt	660
gccaacattt	attactacgg	tggtagctat	gctatggact	actggggtca	aggaacctca	720
gtcaccgtct	cctca					735

<210> SEQ ID NO 391  
 <211> LENGTH: 245  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 391

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

Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr  
 20                25                30

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

Tyr His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly  
 50                55                60

Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln  
 65                70                75                80

Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr  
 85                90                95

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

Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser Thr Lys Gly Glu Val Lys  
 115                120                125

Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser

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130	135	140
Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser		
145	150	155
Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile		
165	170	175
Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu		
180	185	190
Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn		
195	200	205
Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr		
210	215	220
Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser		
225	230	235
Val Thr Val Ser Ser		
245		

<210> SEQ ID NO 392  
 <211> LENGTH: 1383  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 392

atgctgtgc tggtgaccag cctgctgctg tgcgagctgc cccacccgc ctttctgctg	60
atccccgaca tccagatgac ccagaccacc tccagcctga gcgccagcct gggcgaccgg	120
gtgaccatca gctgcccggc cagccaggac atcagcaagt acctgaactg gtatcagcag	180
aagcccgacg gcacccgtcaa gctgctgatc taccacacca gccggctgca cagccggctg	240
cccagccggt ttagccggcag cggctccggc accgactaca gcctgaccat ctccaacctg	300
gaacaggaag atatgccac ctactttgc cagcaggcga acacactgcc ctacaccttt	360
ggccggcggaa caaagctgga aatcacccgc agcacctccg gcagcggcaa gcctggcagc	420
ggcgaggcga gcaccaaggg cgaggtgaag ctgcaggaaa gcccgcctgg cctggtgcc	480
cccagccaga gcctgagcgt gacctgcacc gtgagcggcg tgagcctgcc cgactacggc	540
gtgagctgga tccggcagcc ccccaggaag ggcctggaaat ggctggcgt gatctgggc	600
agcgagacca cctactacaa cagcccccgt aagagccgc tgaccatcat caaggacaac	660
agcaagagcc aggtgttcct gaagatgaac agcctgcaga ccgacgacac cgccatctac	720
tactgcgcca agcaactacta ctacggcggc agctacgcca tggactactg gggccaggc	780
accagcgtga ccgtgagcag cgaatctaag tacggaccgc cctgcccccc ttgcctatg	840
ttctgggtgc tggtggtggt cggaggcgtg ctggcctgct acagcctgct ggtcaccgtg	900
gccttcatca tctttgggt gaaacggggc agaaagaaac tcctgtatat attcaaacaa	960
ccatttatga gaccagtaca aactactcaa gaggaagatg gctgtagctg ccgatttcca	1020
gaagaagaag aaggaggatg tgaactgcgg gtgaagttca gcagaagcgc cgacgcccct	1080
gcctaccagc agggccagaa tcagctgtac aacgagctga acctggcag aagggaaagag	1140
tacgacgtcc tggataagcg gagaggccgg gaccctgaga tggcggcaa gcctcggcgg	1200
aagaacccccc aggaaggcct gtataacgaa ctgcagaaaag acaagatggc cgaggccctac	1260
agcgagatcg gcatgaaggg cgagcggagg cggggcaagg gccacgacgg cctgtatcag	1320
ggcctgtcca cggccaccaa ggatacctac gacgcctgc acatgcagc cctgccccca	1380

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<210> SEQ ID NO 393  
<211> LENGTH: 461  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 393

Met	Leu	Leu	Leu	Val	Thr	Ser	Leu	Leu	Leu	Cys	Glu	Leu	Pro	His	Pro
1							5		10				15		
Ala	Phe	Leu	Leu	Ile	Pro	Asp	Ile	Gln	Met	Thr	Gln	Thr	Thr	Ser	Ser
	20						25			30					
Leu	Ser	Ala	Ser	Leu	Gly	Asp	Arg	Val	Thr	Ile	Ser	Cys	Arg	Ala	Ser
	35				40			45							
Gln	Asp	Ile	Ser	Lys	Tyr	Leu	Asn	Trp	Tyr	Gln	Gln	Lys	Pro	Asp	Gly
	50				55			60							
Thr	Val	Lys	Leu	Leu	Ile	Tyr	His	Thr	Ser	Arg	Leu	His	Ser	Gly	Val
	65				70			75		80					
Pro	Ser	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Tyr	Ser	Leu	Thr
	85				90			95							
Ile	Ser	Asn	Leu	Glu	Gln	Glu	Asp	Ile	Ala	Thr	Tyr	Phe	Cys	Gln	Gln
	100				105			110							
Gly	Asn	Thr	Leu	Pro	Tyr	Thr	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Glu	Ile
	115				120			125							
Thr	Gly	Ser	Thr	Ser	Gly	Ser	Gly	Lys	Pro	Gly	Ser	Gly	Glu	Gly	Ser
	130				135			140							
Thr	Lys	Gly	Glu	Val	Lys	Leu	Gln	Glu	Ser	Gly	Pro	Gly	Leu	Val	Ala
	145				150			155		160					
Pro	Ser	Gln	Ser	Leu	Ser	Val	Thr	Cys	Thr	Val	Ser	Gly	Val	Ser	Leu
	165				170			175							
Pro	Asp	Tyr	Gly	Val	Ser	Trp	Ile	Arg	Gln	Pro	Pro	Arg	Lys	Gly	Leu
	180				185			190							
Glu	Trp	Leu	Gly	Val	Ile	Trp	Gly	Ser	Glu	Thr	Thr	Tyr	Tyr	Asn	Ser
	195				200			205							
Ala	Leu	Lys	Ser	Arg	Leu	Thr	Ile	Ile	Lys	Asp	Asn	Ser	Lys	Ser	Gln
	210				215			220							
Val	Phe	Leu	Lys	Met	Asn	Ser	Leu	Gln	Thr	Asp	Asp	Thr	Ala	Ile	Tyr
	225				230			235		240					
Tyr	Cys	Ala	Lys	His	Tyr	Tyr	Tyr	Gly	Gly	Ser	Tyr	Ala	Met	Asp	Tyr
	245				250			255							
Trp	Gly	Gln	Gly	Thr	Ser	Val	Thr	Val	Ser	Ser	Glu	Ser	Lys	Tyr	Gly
	260				265			270							
Pro	Pro	Cys	Pro	Pro	Cys	Pro	Met	Phe	Trp	Val	Leu	Val	Val	Val	Gly
	275				280			285							
Gly	Val	Leu	Ala	Cys	Tyr	Ser	Leu	Leu	Val	Thr	Val	Ala	Phe	Ile	Ile
	290				295			300							
Phe	Trp	Val	Lys	Arg	Gly	Arg	Lys	Lys	Leu	Leu	Tyr	Ile	Phe	Lys	Gln
	305				310			315		320					
Pro	Phe	Met	Arg	Pro	Val	Gln	Thr	Thr	Gln	Glu	Glu	Asp	Gly	Cys	Ser
	325				330			335							
Cys	Arg	Phe	Pro	Glu	Glu	Glu	Gly	Gly	Cys	Glu	Leu	Arg	Val	Lys	
	340				345			350							

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Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln  
355 360 365

Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu  
370 375 380

Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg  
385 390 395 400

Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met  
405 410 415

Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly  
420 425 430

Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp  
435 440 445

Thr	Tyr	Asp	Ala	Leu	His	Met	Gln	Ala	Leu	Pro	Pro	Arg
						450				455		460

```
<210> SEQ ID NO 394
<211> LENGTH: 801
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide
```

<400> SEQUENCE: 394

atcgctgtgc tggtgaccag cctgctgtc tgcgagtc cccaccccgc cttttgtcg  
atccccgaca tccagatgac ccagaccacc tccagcctga ggcgcaggct gggcgaccgg  
gtgaccatca gctgcggggc cagccaggac atcagcaagt acctgaactg gtatcagcag  
aagccccgacg gcacccgtcaa gctgctgatc taccacacca gcccggctgca cagcggcgtg  
cccgccgggt ttageggcag cggctccggc accgactaca gctgaccat ctccaacctg  
gaacagggaaat atatgccac ctacttttc cagcaggcaca acacactgccc ttttacacc  
ggcgccggaa caaagctgga aatcacccggc agcaccccgcc gcaagccggaa gcccggcc  
ggcgaggggca gcaccaaggcgagggtgaag ctgcaggaaa gcccggccctgg cctggggcc  
cccagccaga gcctgagcgt gacctgcacc gtgagcggcg tgagcctgccc cgactacggc  
gtgagctgga tccggcagcc ccccgaggaa ggcctggaaat ggctggcgt gatctggggc  
agcgagacca cctactacaa cagccggctg aagagccggc tgaccatcat caaggacaac  
agcaagagcc aggtgttcct gaagatgaac agcctgcaga cccgacacac cggccatctac  
tactgcccac agcaactacta ctacggccggc agctacgcca tggactactg gggccaggggc  
accaggcgtga ccgtgagcagc 901

```
<210> SEQ ID NO 395
<211> LENGTH: 267
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide
```

<400> SEQUENCE: 395

Met	Leu	Leu	Leu	Val	Thr	Ser	Leu	Leu	Leu	Cys	Glu	Leu	Pro	His	Pro
1					5					10					15

Leu Ser Ala Ser Leu Gly Asp Arg Val Thr Ile Ser Cys Arg Ala Ser

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35	40	45
Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly		
50	55	60
Thr Val Lys Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Val		
65	70	75 80
Pro Ser Arg Phe Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr		
85	90	95
Ile Ser Asn Leu Glu Gln Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln		
100	105	110
Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile		
115	120	125
Thr Gly Ser Thr Ser Gly Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser		
130	135	140
Thr Lys Gly Glu Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala		
145	150	155 160
Pro Ser Gln Ser Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu		
165	170	175
Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu		
180	185	190
Glu Trp Leu Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser		
195	200	205
Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln		
210	215	220
Val Phe Leu Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr		
225	230	235 240
Tyr Cys Ala Lys His Tyr Tyr Gly Ser Tyr Ala Met Asp Tyr		
245	250	255
Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser		
260	265	

<210> SEQ ID NO 396  
 <211> LENGTH: 1317  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 396

gacatccaga	tgaccaggac	caccccaago	ctgagcgcca	gcctggcgaa	ccgggtgacc	60
atcagctgcc	ggcccgagcc	ggacatcago	aagtacctga	actggtatca	gcagaagccc	120
gacggcaccc	tcaagctgct	gatctaccac	accagccggc	tgcacagccg	cgtccccagc	180
cggtttagcg	cgagcggttc	cgccaccgac	tacagcctga	ccatctccaa	ccttggacag	240
gaagatatacg	ccacctactt	ttgccagcag	ggcaacacac	tgcctacac	cttggccggc	300
ggaacaaagc	tggaaatcac	cggcagcacc	tccggcagcg	gcaagcctgg	cagccggcag	360
ggcagcacca	agggcgaggt	gaagctgcag	gaaagcggcc	ctggcctgg	ggccccccagc	420
cagagcctga	cgctgacactg	caccgtgago	ggcgtgagcc	tgcctgacta	cggcgtgagc	480
tggatccgac	agccccccag	gaagggcctg	gaatggctgg	gcgtgatctg	ggcagcgag	540
accacactact	acaacacgcgc	cctgaagago	cggctgacca	tcatcaagga	caacagcaag	600
agccaggtgt	tcctgaagat	gaacagcctg	cagaccgacg	acaccgccat	ctactactgc	660
gccaaggact	actactacgg	cggcagctac	gccatggact	actggggcca	gggcaccagc	720

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gtgaccgtga gcagcgaatc taagtacgga cccgcctgccccc tatgttctgg	780
gtgctgggtgg tggtcggagg cggtgtggcc tgctacagcc tgctgggtcac cggtggccctc	840
atcatcttt gggtgaaacg gggcagaaag aaactcctgt atatattcaa acaaccattt	900
at gagaccag tacaaactac tcaagaggaa gatggctgtatcgccgatt tccagaagaa	960
gaagaaggag gatgtgaact gcgggtgaag ttccagcagaa ggcggacgc ccctgcctac	1020
cagcaggccc agaatcagct gtacaacagc ctgaacctgg gcagaaggaa agatcagac	1080
gtcctggata agcggagagg ccgggaccct gagatggcg gcaagcctcg gcggaaaac	1140
ccccagggaa gcctgtataa cgaactgcag aaaagacaaga tggccgaggc ctacagcag	1200
atcggcatga agggcgagcg gaggcggggc aagggccacg acggcctgtatcgccgatt	1260
tccaccgcata ccaaggatac ctacgacgcc ctgcacatgc aggccctgcc cccaaagg	1317

&lt;210&gt; SEQ ID NO 397

&lt;211&gt; LENGTH: 439

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 397

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

Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr			
20	25	30	

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

Tyr His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly			
50	55	60	

Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln			
65	70	75	80

Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr			
85	90	95	

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

Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser Thr Lys Gly Glu Val Lys			
115	120	125	

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

Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser			
145	150	155	160

Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile			
165	170	175	

Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu			
180	185	190	

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

Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr			
210	215	220	

Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser			
225	230	235	240

Val Thr Val Ser Ser Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys			
245	250	255	

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Pro Met Phe Trp Val Leu Val Val Gly Gly Val Leu Ala Cys Tyr  
260 265 270

Ser Leu Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val Lys Arg Gly  
275 280 285

Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val  
290 295 300

Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu  
305 310 315 320

Glu Glu Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp  
325 330 335

Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn  
340 345 350

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg  
355 360 365

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly  
370 375 380

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu  
385 390 395 400

Ile Gly Met Lys Gly Glu Arg Arg Gly Lys Gly His Asp Gly Leu  
405 410 415

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His  
420 425 430

Met Gln Ala Leu Pro Pro Arg  
435

<210> SEQ ID NO 398  
<211> LENGTH: 735  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 398

```

gacatccaga tgaccagac cacctccago ctgagcgcca gcctggcga cgggtgacc      60
atcagctgcc gggccagcca ggacatcago aagtacctga actggtatca gcagaagccc    120
gacggcaccc tcaagctgct gatctaccac accagccggc tgcacagccg cgtgeccacg    180
cggtttagcg gcageggctc cggcacccac tacagcttgc ccatctccaa cctggAACAG    240
gaagatatcg ccacctactt ttgccagcg ggAACACAC tgccctacac ctttggccgc    300
ggAACAAAGC tggAAATCAC CGGCAGCACC TCCGGCAGCG GCAAGCCTGG CAGCGGCGAG    360
ggcagcacca agggcgaggt gaagctgcag gaaAGCggcc ctggcctggt ggccccAGC    420
cagagctga gcgtgacctg caccgtgago ggcgtgagcc tgcccgacta cggcgtgagc    480
tggatccggc agccccccAG gaagggctgg gaatggctgg gcgtgatctg gggcagcag    540
accacacct acaacagcgc cctgaagago cggctgacca tcatcaagga caacagcaag    600
agccaggtgt tcctgaagat gaacagcctg cagaccgacg acaccgcat ctactactgc   660
gccaaggact actactacgg cggcagctac gccatggact actggggcca gggcaccAGC   720
gtgaccgtga gcagc                                         735

```

<210> SEQ ID NO 399  
<211> LENGTH: 245  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:

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&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

&lt;400&gt; SEQUENCE: 399

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

Asp	Arg	Val	Thr	Ile	Ser	Cys	Arg	Ala	Ser	Gln	Asp	Ile	Ser	Lys	Tyr			
																20	25	30

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

Tyr	His	Thr	Ser	Arg	Leu	His	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly			
																50	55	60

Ser	Gly	Ser	Gly	Thr	Asp	Tyr	Ser	Leu	Thr	Ile	Ser	Asn	Leu	Glu	Gln				
																65	70	75	80

Glu	Asp	Ile	Ala	Thr	Tyr	Phe	Cys	Gln	Gln	Gly	Asn	Thr	Leu	Pro	Tyr			
																85	90	95

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

Ser	Gly	Lys	Pro	Gly	Ser	Gly	Glu	Gly	Ser	Thr	Lys	Gly	Glu	Val	Lys			
																115	120	125

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

Val	Thr	Cys	Thr	Val	Ser	Gly	Val	Ser	Leu	Pro	Asp	Tyr	Gly	Val	Ser				
																145	150	155	160

Trp	Ile	Arg	Gln	Pro	Pro	Arg	Lys	Gly	Leu	Glu	Trp	Leu	Gly	Val	Ile			
																165	170	175

Trp	Gly	Ser	Glu	Thr	Thr	Tyr	Tyr	Asn	Ser	Ala	Leu	Lys	Ser	Arg	Leu			
																180	185	190

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

Ser	Leu	Gln	Thr	Asp	Asp	Thr	Ala	Ile	Tyr	Tyr	Cys	Ala	Lys	His	Tyr			
																210	215	220

Tyr	Tyr	Gly	Gly	Ser	Tyr	Ala	Met	Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Ser				
																225	230	235	240

Val	Thr	Val	Ser	Ser												
																245

&lt;210&gt; SEQ ID NO 400

&lt;211&gt; LENGTH: 369

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 400

caggtgcagc tgcaggagtc cggcgccggc gtgggtcagc caggccggc cctgagactg 60

tcttgtgcgc ccagcggtt cacttttcc tcttatggca tgcactgggt gagacaggca 120

cctggcaagg gactggagtg ggtggccgtg atctcctacg acggctctaa caagtattac 180

gccgatagcg tgaagggcag gttcaccatc agccgcgaca actccaagaa tacactgtat 240

ctgcagatga atagcctgcg ggccgaggat accgcccgtgt attactgcgg aggctccggc 300

tacgcactgc acgacgattt ttacggactg gacgtgtggg gacagggcac cctggtcaca 360

gtgagctcc 369

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<210> SEQ ID NO 401  
<211> LENGTH: 369  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 401

caggtgcagc tgcaggagtc tggeggagga gtgggtgcagc caggccggtc cctgagactg	60
tcttgcgcgg ccageggctt cacatttct agctacggaa tgcactgggt gcccaggca	120
cctggcaagg gactggagtg ggtggccgtg atctcctatg acggctctaa caagtactat	180
gccgattccg tgaagggcag gttaccatc agccgcgaca actccaagaa tacactgtac	240
ctgcagatga attccctgcg ggccgaggat accggccgtg actattgtgg cggctctggc	300
tatgcctgc acgacgatta ctatggactg gacgtgtggg gacagggcac cctggtgaca	360
gtgtcctct	369

<210> SEQ ID NO 402  
<211> LENGTH: 369  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 402

caggtgcagc tgcaggagtc tggeggagga gtgggtgcagc caggccggag cctgagactg	60
tcctgcgcgg cctctggctt cacctttagc tcctatggca tgcactgggt gagacaggca	120
cctggcaagg gactggagtg ggtggccgtg atcagctacg acggctccaa caagtattac	180
gccgatacg tgaagggcag gttaccatc tctcgcgaca acagcaagaa tacactgtat	240
ctgcagatga attccctgcg ggccgaggat acagccgtg attactgcgg aggccggc	300
tacgcactgc acgacgatta ttacggactg gacgtgtggg gacagggcac cctggtcaca	360
gtgtcttagc	369

<210> SEQ ID NO 403  
<211> LENGTH: 369  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 403

caggtgcagc tgcaggagag cgccggccgc gtgggtgcagc cggccggtc tctgagactg	60
agctgtgcgg cctccggctt cacctttagc tcctacggaa tgcactgggt gcccaggca	120
cctggcaagg gactggagtg ggtggccgtg atctcctatg acggcagcaa caagtactat	180
gccgatacg tgaagggcag gttaccatc tcccgcgaca actctaagaa tacactgtac	240
ctgcagatga atacgcctgcg ggccgaggat accggccgtg actattgcgg aggctccggc	300
tatgcactgc acgacgatta ctatggactg gacgtgtggg gacagggcac cctggtgaca	360
gtgtcttagc	369

<210> SEQ ID NO 404  
<211> LENGTH: 369  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 404

```
caggtccagc tgcaggagag tggggggggg gtcgtccagc ccggaagaag cctgagactg      60
tcatgtgcgc catctgggtt taccttttagc tcctatggaa tgcactgggt gcgccaggca     120
cctggcaagt gcctggagtg ggtggccgtg atctcctacg acggctctaa caagtactat     180
gccgatagcg tgaagggccg gttaccattc agcagagaca actccaagaa tacactgtat     240
ctgcagatga attctctgcg ggccgaggat accggccgtg actattgtgg aggctccggc     300
tacgcactgc acgacgatta ctatggactg gacgtgtggg gacagggcac cctggtgaca     360
gtgtcttagc                                         369
```

<210> SEQ ID NO 405

<211> LENGTH: 369  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 405

```
caggtccagc tgcaggatac cgggggagga gtgggtgcagc caggccggtc tctgagactg      60
agctgcgcgc cttccggctt cacatttcc tcttatggca tgcactgggt gagacaggcc     120
cctggcaagt gtctggagtg ggtggccgtg atctcctacg acggcagcaa caagtattac     180
gccgatagcg tgaagggcag gttaccattc tcccgccgaca actctaagaa tacactgtat     240
ctgcagatga attccctgcg ggccgaggat accggccgtg attactgtgg cggctctggc     300
tacgcactgc acgacgacta ctatggactg gatgtctggg ggcagggcac actggtcact     360
gtctcttca                                         369
```

<210> SEQ ID NO 406

<211> LENGTH: 369  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 406

```
caggtccagc tgcaggatac aggggggggg gtcgtccagc ccggaagaag tctgagactg      60
tcatgtgcgc catcagggtt taccttttagc tcctatggaa tgcactgggt gcgccaggca     120
cctggcaagt gcctggagtg ggtggccgtg atctcctacg acggctctaa caagtactat     180
gccgatagcg tgaagggccg gttaccattc agcagagaca actccaagaa tacactgtat     240
ctgcagatga attctctgcg ggccgaggat accggccgtg actattgtgg aggctccggc     300
tacgcactgc acgacgatta ctatggactg gacgtgtggg gacagggcac cctggtgaca     360
gtgtcttagc                                         369
```

<210> SEQ ID NO 407

<211> LENGTH: 369  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

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&lt;400&gt; SEQUENCE: 407

cagggtccagc	tgcaggaatc	cgggggagga	gtgggtgcagc	caggccggtc	tctgagactg	60
agctgcgcgc	cctccggctt	cacctttcc	tcttatggca	tgcactgggt	gagacaggcc	120
cctggcaagt	gtctggagtg	ggtggccgtg	atctcttacg	acggcagcaa	caagtattac	180
gccgatagcg	tgaagggcag	gttaccatc	tcccgcgaca	actctaagaa	tacactgtat	240
ctgcagatga	attccctgcg	ggcggaggat	acagccgtgt	attactgtgg	cggctctggc	300
tacgcccctgc	atgatgatta	ttatggactg	gatgtctggg	ggcagggcac	actggtcact	360
gtctcttcc						369

&lt;210&gt; SEQ ID NO 408

&lt;211&gt; LENGTH: 333

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 408

cagtctgccc	tgacccagcc	agcaagcgtg	tccggctctc	ctggccagag	catcacaatc	60
tcttgacccg	gcacaagctc	cgacgtggga	ggctataact	acgtgagctg	gtatcagcag	120
caccggca	aggcccccaa	gctgtatgatc	tacgacgtga	gcaacaggcc	ttctggcgtg	180
agcaatcgct	tcagcggctc	caagtctggc	aataccgcct	ctctgacaat	cagcggcctg	240
caggcagagg	acgaggcaga	ttattactgc	tctagctata	cctccctctag	cacactgtac	300
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&lt;210&gt; SEQ ID NO 409

&lt;211&gt; LENGTH: 333

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 409

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caccctggca	aggccccaaa	gctgtatgatc	tatgacgtga	gcaacaggcc	atccggcgtg	180
tctaataatag	tctccggctc	taagagcggc	aataccgcct	ccctgacaat	ctctggcctg	240
caggcagagg	acgaggcaga	ttactattgt	tctagctaca	cctccctctag	cacactgtac	300
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&lt;210&gt; SEQ ID NO 410

&lt;211&gt; LENGTH: 333

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 410

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caccggca	aggcccccaa	gctgtatgatc	tacgatgtga	gcaacaggcc	ttctggcgtg	180

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agcaatcgct tcagcggctc caagtctggc aataccgcca gcctgacaat ctccggcctg	240
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<210> SEQ ID NO 411  
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caccctggca aggccccaaa gctgtatgtatc tatgtatgtga gcaaccggcc ctccggcctg	180
tctaataatgc tctccggctc taagagcggc aataccgcca gcctgacaat ctccggcctg	240
caggcagagg acgaggcaga ttactattgc tcctcttaca ccagcttctc tacactgtac	300
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<210> SEQ ID NO 412  
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caccctggca aggccccaaa gctgtatgtatc tacgacgtga gcaaccggcc ctctggcctg	180
agcaatcggt tcagcggcag caagtctggc aataccgccc ccctgacaat ctctggcctg	240
caggcagagg acgaggcaga ttattactgtt agcagttata ctcaagctc aaccctgtac	300
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caccctggca aggccccaaa gctgtatgtatc tacgacgtga gcaacaggcc atctggcctg	180
agcaatcggt tcagcggctc caagtctggc aataccgcca gcctgacaat ctccggcctg	240
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<210> SEQ ID NO 414  
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<212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence  
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<400> SEQUENCE: 414

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caccctggca	aggccccaaa	gctgtatgatc	tacgacgtga	gcaacccggcc	ctctggcgtg	180
agcaatcggt	tcagcggcag	caagtctggc	aataccgcct	ccctgacaat	ctctggcctg	240
caggcagagg	acgaggcaga	ttattactgt	agtccttaca	cttcttcaag	cacactgtat	300
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<210> SEQ ID NO 415  
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 415

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caccctggca	aggcccccaa	gctgtatgatc	tacgacgtga	gcaacaggcc	ttctggcgtg	180
agcaatcgct	tcagcggcctc	caagtctggc	aataccgcct	gcctgacaat	ctccggcctg	240
caggcagagg	acgaggcaga	ttactattgc	agtccttata	cctcttagctc	cacactgtac	300
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<400> SEQUENCE: 416

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ccgcaggatc	aattgcagga	gtctggaggc	ggtgtgggtc	aacccggctcg	cagttgcgc	120
ctgagttgtg	ctgcgtctgg	atttacattt	tcatcttacg	aatgcatttgc	ggtacgcac	180
gcaccgggaa	aaggccttga	atgggtggct	gtatattcat	acgtatggtcc	caacaatac	240
tatgctact	cagtcaaggg	tcgatttaca	attagtcggg	acaactccaa	gaacaccctt	300
tatcttcaaa	tgaattccct	tagagcagag	gatacggccg	tctattactg	tggtggcagt	360
ggtttatgcac	ttcatgtatg	ttactatggc	ttggatgtct	gggggcagg	gacgcttgta	420
actgtatctt	ctgggtggtg	tggttagtggt	gggggaggct	ccggcggtgg	cggtctcaa	480
tctgctctga	ctcaaccaggc	aagcgatctca	gggtcacccgg	gacagagtat	taccataagt	540
tgcacgggaa	cctcttagcga	tgttaggggg	tataattatg	tatcttgta	tcaacaacac	600
cccggggaaag	cccctaatt	gatgtatctac	gacgtgagca	atcgacctag	tggcgatctca	660
aatcgcttct	ctggtagcaa	gagtggaaat	acggcgtccc	ttactattag	cggattgcaa	720
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792

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tttgggagcg gaacaaaagt aacagtactc acaacaacac ctgccccgag accgectaca	840
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gcggggcggcg cagttcatac acggggcttg gattpcgctt gtgatattta tatttggct	960
cctttgggg ggacatgtgg cgtgtgtctt ctgtcacttg ttattacact gtactgtaaa	1020
cgccggcggaa aaaaattgct gtatatttt aagcagccat ttatgaggcc cggtcagacg	1080
acgcaggagg aggacggttg ctcttcagg ttcccagaag aggaagaagg gggctgtgaa	1140
ttgcgggtta aattttcaag atcccgagac gctccagcat accaacaggg acaaaaccaa	1200
ctctataacg actgtaatct tggagaagg gagaaatatg atgtgtggtaaaacggcgc	1260
ggtagagatc cggagatggg cggaaaacca aggcgaaaaa accctcagga gggactctac	1320
aacgaactgc agaaagacaa aatggcggag gcttattccg aaataggcat gaagggcag	1380
cggaggcggag ggaaaggcga cgacggactg tatcaaggcc tctcaaccgc gactaaggat	1440
acgtacgacg ccctgcacat gcaggccctg cctccgagat gataa	1485

&lt;210&gt; SEQ ID NO 417

&lt;211&gt; LENGTH: 1395

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

&lt;400&gt; SEQUENCE: 417

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ggacaggctc ctcgccttct gatctaccac accagccggc tccattctgg aatccctgcc	180
aggttcagcg gtagcggatc tgggaccgac tacaccctca ctatcagctc actgcagcca	240
gaggacttcg ctgtcttattt ctgtcagcaa gggAACACCC tgccctacac ctttggacag	300
ggcaccaagg tcgagattaa aggtggaggt ggcagcggag gaggtgggtc cggcggtgga	360
ggaagccagg tccaactcca agaaaaggcga cccgggttgg tgaaggccatc agaaaacttt	420
tcaactgactt gtactgtgag cggagtgtct ctccccgatt acgggggtgtc ttggatcaga	480
cagccacccgg ggaagggtct ggaatggatt ggagtgatt ggggctctga gactacttac	540
taccaatcat ccctcaagtc acgegtcacc atctcaaagg acaactctaa gaatcaggtg	600
tcactgaaac tgcgtatctgt gaccgcagec gacaccggcg tgcgtatctg cgctaagcat	660
tactattatg gcgggagcta cgcaatggat tactggggac agggtaactct ggtcaccgtg	720
tccagcacca ctaccccaagc accgaggcga cccaccccg ctcctaccat cgcccccag	780
cctctgtccc tgcgtccggc ggcgttgcgaa cccgcagctg gtggggccgt gcataccgg	840
ggtcttgcgtt tgcgttgcgtt tatctacatt tggcccttc tggctggat ttgcgggtc	900
ctgtgtttt cactcgtgtat cacttttac tgcgttgcgtt gtcggaaagaa gtcgtgtac	960
atctttaaatc aacccttcat gaggctgtg cagactactc aagaggagga cggctgttca	1020
tgcgggttcc cagaggagga ggaaggcggc tgcgttgcgtt gtcggaaatt cagccgcagc	1080
gcagatgttc cagctacca gcaggggcag aaccagctct acaacgaact caatcttgcgtt	1140

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cgagagagg agtacgacgt gctggacaag cggagaggac gggaccaga aatggggggg	1200
aagccgcga gaaagaatcc ccaagaggc ctgtacaacg agctccaaa ggataagatg	1260
gcagaagct atagcgagat tggtatgaaa ggggaacgca gaagaggcaa aggccacgac	1320
ggactgtacc agggactcag caccgccacc aaggacacct atgacgctct tcacatgcag	1380
gcctgcgc ctcgg	1395

What is claimed is:

1. An isolated cell or a population of cells comprising a polypeptide comprising:

(a) a first chimeric antigen receptor (CAR) comprising a first antigen-binding domain which binds to BCMA (a BCMA CAR) and a first transmembrane domain; a first intracellular signaling domain comprising a co-stimulatory signaling domain and a first primary signaling domain;

and

(b) a second CAR comprising a second antigen-binding domain which binds to CD19 (a CD19 CAR) and a second transmembrane domain; a second intracellular signaling domain comprising a second co-stimulatory signaling domain; and a second primary signaling domain;

wherein the first CAR and the second CAR each comprise an HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 as recited in one of SEQ ID NO: 214, 216, 218, 220, or 222.

2. The isolated cell or population of cells of claim 1, wherein the first CAR is encoded by a first nucleic acid sequence and the second CAR is encoded by a second nucleic acid sequence, wherein the first and second nucleic acid sequences are disposed on a single nucleic acid molecule.

3. The isolated cell or population of cells of claim 2, wherein:

(a) the single nucleic acid molecule comprises the following configuration in a 5' to 3' orientation:

(i) a nucleic acid sequence encoding the first antigen-binding domain-a nucleic acid sequence encoding a first transmembrane domain-a nucleic acid sequence encoding a first intracellular signaling domain-a nucleic acid sequence encoding a linker-a nucleic acid sequence encoding the second antigen-binding domain-a nucleic acid sequence encoding a second transmembrane domain-a nucleic acid sequence encoding a second intracellular signaling domain; or

(ii) a nucleic acid sequence encoding the second antigen-binding domain-a nucleic acid sequence encoding a second transmembrane domain-a nucleic acid sequence encoding a second intracellular signaling domain-a nucleic acid sequence encoding a linker-a nucleic acid sequence encoding the first antigen-binding domain-a nucleic acid sequence encoding a first transmembrane domain-a nucleic acid sequence encoding a first intracellular signaling domain;

(b) the single nucleic acid molecule comprises the nucleic acid sequence of SEQ ID NO: 215, 217, 219, 221, or 223, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto; or

(c) the single nucleic acid molecule encodes the amino acid sequence of SEQ ID NO: 214, 216, 218, 220, or

222, or an amino acid sequence having at least about 95%, or 99% sequence identity thereto.

4. The isolated cell or population of cells of claim 1, wherein the first antigen-binding domain or second antigen-binding domain comprises a VH and a VL, wherein the VH and VL are connected by a linker, and wherein the linker comprises the amino acid sequence of SEQ ID NO: 5, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.

5. The isolated cell or population of cells of claim 2, wherein:

(i) the first transmembrane domain or second transmembrane domain comprises the amino acid sequence of SEQ ID NO: 6, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto;

(ii) the first transmembrane domain or second transmembrane domain is encoded by the nucleic acid sequence of SEQ ID NO: 17, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto;

(iv) the first antigen-binding domain is connected to the first transmembrane domain by a first hinge region or the second antigen-binding domain is connected to the second transmembrane domain by a second hinge region;

(v) the primary signaling domain comprises a functional signaling domain derived from a CD3 zeta, wherein;

(a) the primary signaling domain comprises the amino acid sequence of SEQ ID NO: 9 or 10, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto; or

(b) the primary signaling domain is encoded by the nucleic acid sequence of SEQ ID NO: 20, 21, or 205, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto;

(vi) the costimulatory signaling domain comprises a functional signaling domain derived from 4-1BB (CD137); wherein:

(a) the costimulatory signaling domain comprises the amino acid sequence of SEQ ID NO: 7, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto; or

(b) the costimulatory signaling domain is encoded by the nucleic acid sequence of SEQ ID NO: 18 or 204, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto;

(vii) the first intracellular signaling domain or second intracellular signaling domain comprises a functional signaling domain derived from 4-1BB and a functional signaling domain derived from CD3 zeta, wherein:

(a) the first intracellular signaling domain or second intracellular signaling domain comprises the amino acid sequence of SEQ ID NO: 7 (or an amino acid sequence having at least about 85%, 90%, 95%, or 99%

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- sequence identity thereto) and the amino acid sequence of SEQ ID NO: 9 or 10 (or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto), or
- (b) the first intracellular signaling domain or second intracellular signaling domain comprises the amino acid sequence of SEQ ID NO: 7 and the amino acid sequence of SEQ ID NO: 9 or 10; or
  - (viii) the first CAR further comprises a first leader sequence or second CAR further comprises a second leader sequence, wherein:
    - (a) the first or second leader sequence comprises the amino acid sequence of SEQ ID NO: 1, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto; or
    - (b) the first or second leader sequence is encoded by the nucleic acid sequence of SEQ ID NO: 199 or 210, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.
6. The isolated cell or population of cells of claim 2, wherein:
- (a)
    - (i) the first leader sequence and the second leader sequence are encoded by different nucleic acid sequences;
    - (ii) the first hinge region and the second hinge region are encoded by different nucleic acid sequences;
    - (iii) the first transmembrane domain and the second transmembrane domain are encoded by different nucleic acid sequences; and/or
    - (iv) the first intracellular signaling domain and the second intracellular signaling domain are encoded by different nucleic acid sequences;
  - (b)
    - (i) the first leader sequence and the second leader sequence comprise the same amino acid sequence, or comprise different amino acid sequences;
    - (ii) the first hinge region and the second hinge region comprise the same amino acid sequence, or comprise different amino acid sequences;
    - (iii) the first transmembrane domain and the second transmembrane domain comprise the same amino acid sequence, or comprise different amino acid sequences; and/or
    - (iv) the first intracellular signaling domain and the second intracellular signaling domain comprise the same amino acid sequence, or comprise different amino acid sequences;
  - (c)
    - (i) the first leader sequence and the second leader sequence are encoded by nucleic acid sequences comprising SEQ ID NOS: 199 and 210, respectively, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto, or SEQ ID NOS: 210 and 199, respectively, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto;
    - (ii) the first hinge region and the second hinge region are encoded by nucleic acid sequences comprising SEQ ID NOS: 337 and 13, respectively, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto; or SEQ ID NOS: 13 and 337, respectively, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto;
    - (iii) the first transmembrane domain and the second transmembrane domain are encoded by nucleic acid

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- sequences comprising SEQ ID NOS: 338 and 17, respectively, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto; or SEQ ID NOS: 17 and 338, respectively, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto;
- (iv) the first costimulatory signaling domain and the second costimulatory signaling domain are encoded by nucleic acid sequences comprising SEQ ID NOS: 204 and 18, respectively, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto; or SEQ ID NOS: 18 and 204, respectively, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto; and/or
  - (v) the first primary signaling domain and the second primary signaling domain are encoded by nucleic acid sequences comprising SEQ ID NOS: 205 and 21, respectively, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto; or SEQ ID NOS: 21 and 205, respectively, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto; or
  - (d) the first CAR or second CAR is encoded by a nucleic acid molecule comprising a woodchuck hepatitis post-transcriptional regulatory element (WPRE).
7. An isolated nucleic acid molecule encoding a polypeptide, said nucleic acid molecule comprising:
- (a) a first nucleic acid sequence encoding a first CAR comprising a first antigen-binding domain which binds to BCMA (a BCMA CAR) and a first transmembrane domain; a first intracellular signaling domain comprising a co-stimulatory signaling domain and a first primary signaling domain; and
  - (b) a second nucleic acid sequence encoding a second CAR comprising a second antigen-binding domain which binds to CD19 (a CD19 CAR) and a second transmembrane domain; a second intracellular signaling domain comprising a second co-stimulatory signaling domain; and a second primary signaling domain; wherein the first CAR and the second CAR each comprise an HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 as recited in one of SEQ ID NO: 214, 216, 218, 220, or 222;
- and  
wherein  
the first nucleic acid sequence and the second nucleic acid sequence are disposed on a single nucleic acid molecule.
8. An isolated polypeptide, wherein the polypeptide comprises:
- (a) a first CAR comprising a first antigen-binding domain which binds to BCMA (a BCMA CAR) and a first transmembrane domain; a first intracellular signaling domain comprising a co-stimulatory signaling domain and a first primary signaling domain; and
  - (b) a second CAR comprising a second antigen-binding domain which binds to CD19 (a CD19 CAR) and a second transmembrane domain; a second intracellular signaling domain comprising a second co-stimulatory signaling domain; and a second primary signaling domain; and  
wherein the first CAR and the second CAR each comprise an HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 as recited in one of SEQ ID NO: 214, 216, 218, 220, or 222.

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9. A vector comprising the nucleic acid molecule claim 7.  
 10. An isolated cell or a population of cells comprising the nucleic acid molecule of claim 7.

11. A method of making a cell comprising transducing a cell with the vector of claim 9.

12. A method of making an RNA-engineered cell comprising introducing an in vitro transcribed RNA or synthetic RNA into a cell, wherein the RNA comprises the nucleic acid molecule of claim 7.

13. A pharmaceutical composition comprising the cell or population of cells of claim 1, and a pharmaceutically acceptable carrier.

14. A population of cells engineered to express the polypeptide of claim 8,

wherein the population comprises a cell comprising a nucleic acid molecule encoding the first CAR and the second CAR, and wherein:

the nucleic acid molecule comprises a first nucleic acid sequence encoding the first CAR and a second nucleic acid sequence encoding the second CAR, or

the first and second nucleic acid sequences are disposed on a single nucleic acid molecule, wherein the first nucleic acid sequence and the second nucleic acid sequence are separated by a third nucleic acid sequence 25  
encoding a self-cleavage site.

15. The isolated cell of claim 3, wherein the linker comprises a self-cleavage site, and wherein the self-cleavage site comprises a P2A site, a T2A site, an E2A site, or an F2A site.

16. The isolated cell of claim 15, wherein:

(a) the linker is encoded by the nucleic acid sequence of SEQ ID NO: 209, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto; or

(b) the linker comprises the amino acid sequence of SEQ ID NO: 208, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.

17. The isolated cell of claim 5, wherein:

(a) the first hinge region or the second hinge region comprises the amino acid sequence of SEQ ID NO: 2, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto;

(b) the first hinge region or the second hinge region is encoded by the nucleic acid sequence of SEQ ID NO: 13, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto;

(c) the first hinge region and the first transmembrane domain or the second hinge region and the second transmembrane domain and the transmembrane domain comprise the amino acid sequence of SEQ ID NO: 202,  
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or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto; or

(d) the first hinge region and the first transmembrane domain or the second hinge region and the second transmembrane domain and the transmembrane domain are encoded by the nucleic acid sequence of SEQ ID NO: 203 or 213, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.

18. The isolated cell of claim 6, wherein:

(a) the first primary signaling domain and the second primary signaling domain are encoded by different nucleic acid sequences;

(b) the first costimulatory signaling domain and the second costimulatory signaling domain are encoded by different nucleic acid sequences;

(c) the first leader sequence and the second leader sequence comprise the amino acid sequence of SEQ ID NO: 1, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto;

(d) the first hinge region and the second hinge region comprise the amino acid sequence of SEQ ID NO: 2, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto;

(e) the first transmembrane domain and the second transmembrane domain comprise the amino acid sequence of SEQ ID NO: 6, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto;

(f) the first primary signaling domain and the second primary signaling domain comprise the amino acid sequence of SEQ ID NO: 10, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto; or

(g) the first costimulatory signaling domain and the second costimulatory signaling domain comprise the amino acid sequence of SEQ ID NO: 7, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.

19. The vector of claim 9, wherein the vector is chosen from a DNA vector, a RNA vector, a plasmid, a lentivirus vector, an adenoviral vector, or a retrovirus vector.

20. The isolated nucleic acid molecule of claim 7, wherein the encoded polypeptide comprising the first CAR and the second CAR comprises the amino acid sequence of SEQ ID NO: 214, 216, 218, 220, 222, or an amino acid having at least 95%, 96%, 97%, 98%, or 99% identity thereto.

21. The isolated polypeptide of claim 8, wherein the polypeptide comprises the amino acid sequence of SEQ ID NO: 214, 216, 218, 220, 222, or an amino acid having at least 95%, 96%, 97%, 98%, or 99% identity thereto.

\* \* \* \* \*