

**MEMBRANE-BOUND IL-15, CD8 POLYPEPTIDES, CELLS,
COMPOSITIONS, AND METHODS OF USING THEREOF**

RELATED APPLICATIONS

[0001] The present application is an International Application claiming priority to U.S. Provisional Patent Application No. 63/336,025, filed on April 28, 2022, the entire contents of which are hereby incorporated by reference for all purposes.

REFERENCE TO SEQUENCE LISTING SUBMITTED ELECTRONICALLY

[0002] The official copy of the sequence listing is submitted concurrently via EFS-Web as an ASCII-formatted sequence listing with a file named “3000011-029977_Sequence-Listing_ST26” created on April 27, 2023, and having a size of 722,707 bytes, and is filed concurrently with the specification. The sequence listing contained in this ASCII-formatted document is part of the specification and is herein incorporated by reference in its entirety.

BACKGROUND

Field

[0003] The present disclosure relates to cells capable of co-expressing one or any combination of T cell receptors (“TCR”), CD8 polypeptides, and/or membrane-bound interleukin 15 (IL-15) and the use thereof in adoptive cellular therapy (“ACT”). The present disclosure further provides for modified CD8 sequences, IL-15 sequences, IL-15 receptor α (IL-15-R α) sequences, IL-15/IL-15R α fusion polypeptides, vectors, compositions, transformed cells, and associated methods thereof.

Background

[0004] CD8 and CD4 are transmembrane glycoproteins characteristic of distinct populations of T lymphocytes whose antigen responses are restricted by class I and class II MHC molecules, respectively. They play major roles both in the differentiation and selection of T cells during thymic development and in the activation of mature T lymphocytes in response to antigen presenting cells. Both CD8 and CD4 are immunoglobulin superfamily proteins. They determine antigen restriction by binding to MHC molecules at an interface distinct from the region presenting the antigenic peptide, but the structural basis for their similar functions appears to be very different. Their sequence similarity is low and, whereas CD4 is expressed on the cell surface as a monomer, CD8 is expressed as an $\alpha\alpha$ homodimer (e.g., FIG. 55C) or an $\alpha\beta$ heterodimer (e.g., FIG. 55A). In humans, this CD8 $\alpha\alpha$ homodimer may functionally substitute for

the CD8 $\alpha\beta$ heterodimer. CD8 contacts an acidic loop in the $\alpha 3$ domain of Class I MHC, thereby increasing the avidity of the T cell for its target. CD8 is also involved in the phosphorylation events leading to CTL activation through the association of its α chain cytoplasmic tail with the tyrosine kinase p56^{lck}.

[0005] Pleiotropic cytokine interleukin-15 (“IL-15” or “IL15”) is a member of the 4 α -helix bundle cytokine family. (Waldmann TA and Tagaya Y, *Ann. Rev. Immunol.* 17: 19-49, 1999, the content of which is incorporated herein by reference). A 14-15 kDa glycoprotein, wild type IL-15 shares partial structural homology with IL-2. (*Id.*). Wild type IL-15 can be expressed in two isoforms, one having a 48 amino acid signal peptide and the other having a 21 amino acid signal peptide. (*Id.*). The mature form of wild type IL-15 consists of 114 amino acids. (*Id.*). Wild type IL-15 expression is regulated at the transcriptional, translational, and intracellular trafficking levels. (*Id.*). Wild type IL-15 utilizes a private receptor, IL-15R α (or “IL15R α ”), which, in lymphocytes, binds IL-15 with high affinity and trimerizes with IL-2R β (also referred to as IL-2/IL-15R β) and IL-2R γ (also referred to as γ_c). (*Id.*; Okada S et al., *Immunol. and Cell Biol.* 93: 461-471, 2015, the content of which is incorporated herein by reference). Wild type IL-15R α comprises a signal peptide, an extracellular domain, a transmembrane domain, and a cytoplasmic domain. (Waldman and Tagaya). The extracellular domain of wild type IL-15R α comprises a sushi domain (also referred to as a GP-1 motif). (*Id.*).

[0006] Adoptive cell therapy (ACT) is a promising approach to treatment of diseases such as cancer. T-cell therapy has been successful in treating various cancers. Li *et al.* *Signal Transduction and Targeted Therapy* 4(35): (2019), the content of which is incorporated by reference in its entirety. However, cells used in ACT often fail to persist in the tumor microenvironment and quickly lose their ability to kill tumor cells. Accordingly, there is a need for T cells and natural killer cells that exhibit longer persistence in the tumor microenvironment and/or sustained capability to kill tumor cells. It is also desirable to develop methods of manufacturing T cells and natural killer cells with enhanced, specific cytotoxic activity for immunotherapy.

BRIEF SUMMARY

[0007] In embodiments, a membrane-bound IL-15 polypeptide (membrane-bound IL-15 or mbIL-15) may be provided. In embodiments, nucleic acids described herein may comprise and/or encode a membrane-bound IL-15 polypeptide. In embodiments, vectors described herein may comprise and/or encode a membrane-bound IL-15 polypeptide. In embodiments, cells described herein may comprise and/or express a membrane-bound IL-15 polypeptide. In embodiments, compositions described herein may comprise a membrane-bound IL-15

polypeptide or may comprise cells comprising and/or expressing a membrane-bound IL-15 polypeptide. In embodiments, IL-15 may be rendered membrane-bound by expressing an IL-15 polypeptide and an IL-15R α polypeptide in an IL-15/IL-15R α fusion polypeptide (IL-15/IL-15R α). IL-15/IL-15R α fusion polypeptides and other membrane-bound forms of IL-15 may be referred to as membrane-bound IL-15 (mbIL-15).

[0008] In embodiments, isolated membrane-bound IL-15 polypeptides may be provided. Isolated nucleic acid sequences comprising one or more nucleic acid sequences encoding one or more membrane-bound IL-15 polypeptides may be provided. In embodiments, isolated vectors comprising one or more nucleic acid sequences comprising one or more nucleic acid sequences encoding one or more membrane-bound IL-15 polypeptides may be provided. In embodiments, cells comprising and/or expressing one or more membrane-bound IL-15 polypeptides may be provided. In embodiments, cells comprising or expressing one or more nucleic acid sequences comprising one or more nucleic acid sequences encoding one or more membrane-bound IL-15 polypeptides may be provided. In embodiments, cells comprising or expressing one or more vectors comprising one or more nucleic acid sequences comprising one or more nucleic acid sequences encoding one or more membrane-bound IL-15 polypeptides may be provided. In embodiments, compositions comprising such polypeptides, nucleic acids, vectors, and/or cells may be provided.

[0009] In embodiments, an IL-15 polypeptide may be located N-terminal to an IL-15R α polypeptide in a membrane-bound IL-15 polypeptide. (FIG. 67A). In embodiments, an IL-15 polypeptide may be located C-terminal to an IL-15R α polypeptide in a membrane-bound IL-15 polypeptide. (FIG. 67B). The IL-15 polypeptide in FIGS. 67A and 67B may be immature wild type ("wt"), immature mutated, mature wild type, or mature mutated. The IL-15R α polypeptide in FIGS. 67A and 67B may be immature wild type, immature mutated, mature wild type, or mature mutated. In embodiments, the IL-15 polypeptide in 67A and 67B is mature and may or may not be mutated, and the IL-15R α polypeptide in 67A and 67B is mature and may or may not be mutated. In embodiments, the IL-15 polypeptide in 67A and 67B is mature and may or may not be mutated, and the IL-15R α polypeptide in in 67A and 67B is mature and mutated. Although a linker is depicted in FIGS: 67A and 67B, a mbIL-15 polypeptide may or may not comprise a linker.

[0010] In embodiments, an IL-15 polypeptide and an IL-15R α polypeptide may be linked by one or more linker. In embodiments, a membrane-bound IL-15 may comprise and/or be encoded by a structure as shown in FIG. 67A or FIG. 67B. In FIGs. 67A and 67B, the lines connecting the IL-15 to the one or more linker (L) and the one or more linker (L) to the IL-15R α may represent direct linkages, with no intervening sequences, or may represent intervening

sequences, such as, but not limited to, a linker, an untranslated sequence (in the case of a nucleic acid sequence), a translated sequence, a sequence comprising one or more restriction endonuclease sites (in the case of a nucleic acid sequence), or a combination thereof.

[0011] In embodiments, an IL-15/IL-15R α polypeptide may comprise one or more signal peptide. In embodiments, a membrane-bound IL-15 comprising one or more signal peptide and, optionally, one or more linker may comprise and/or be encoded by a structure as shown in FIG. 68A or FIG. 68B. The IL-15 polypeptide in FIGS. 68A and 68B may be immature wild type, immature mutated, mature wild type, or mature mutated. The IL-15R α polypeptide in FIGS. 68A and 68B may be immature wild type, immature mutated, mature wild type, or mature mutated. In embodiments, the IL-15 polypeptide in FIG. 68A and FIG. 68B is mature and may or may not be mutated, and the IL-15R α polypeptide in FIG. 68A and FIG. 68B is mature and may or may not be mutated. In embodiments, the IL-15 polypeptide in FIG. 68A and FIG. 68B is mature and may or may not be mutated, and the IL-15R α polypeptide in FIG. 68A and FIG. 68B is mature and mutated. Although a linker is depicted in FIGS. 68A and 68B, a mbIL-15 polypeptide comprising a signal peptide may or may not comprise a linker. In FIGS. 68A and 68B, the lines connecting (a) the one or more signal peptide (SP) to the IL-15, the IL-15 to the one or more linker (L), and the one or more linker to the IL-15R α (as in FIG. 68A) or (b) the one or more signal peptide (SP) to the IL-15 α , the IL-15 α to the one or more linker (L), and the one or more linker to the IL-15 (as in FIG. 68B) may represent direct linkages, with no intervening sequences, or may represent intervening sequences, such as, but not limited to, a linker, an untranslated sequence (in the case of a nucleic acid sequence), a translated sequence, a sequence comprising one or more restriction endonuclease sites (in the case of a nucleic acid sequence), or a combination thereof.

[0012] In embodiments, CD8 polypeptides described herein may comprise a CD8 α immunoglobulin (Ig)-like domain, a CD8 β region, a CD8 α transmembrane domain, and a CD8 α cytoplasmic domain. In embodiments, a CD8 β region may be a CD8 β stalk region or domain.

[0013] In embodiments, CD8 polypeptides described herein may comprise (a) an immunoglobulin (Ig)-like domain comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the amino acid sequence of SEQ ID NO: 1, (b) a CD8 β region comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identity sequence identity to the amino acid sequence of SEQ ID NO: 2, (c) a transmembrane domain

comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the amino acid sequence of SEQ ID NO: 3, and (d) a cytoplasmic domain comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the amino acid sequence of SEQ ID NO: 4.

[0014] In embodiments, CD8 polypeptides described herein have at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the amino acid sequence of SEQ ID NO: 5.

[0015] In embodiments, CD8 polypeptides described herein have at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the amino acid sequence of SEQ ID NO: 7.

[0016] In embodiments, CD8 polypeptides described herein may comprise one or more signal peptide with at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the amino acid sequence of any one of SEQ ID NO: 6, SEQ ID NO: 293, or SEQ ID NO: 294 directly or indirectly fused to the N-terminus or to the C-terminus of CD8 polypeptides described herein.

[0017] In embodiments, CD8 polypeptides described herein may comprise (a) SEQ ID NO: 1 comprising one, two, three, four, or five amino acid substitutions; (b) SEQ ID NO: 2 comprising one, two, three, four, or five amino acid substitutions; (c) SEQ ID NO: 3 comprising one, two, three, four, or five amino acid substitutions, and (d) SEQ ID NO: 4 comprising one, two, three, four, or five amino acid substitutions. In embodiments, amino acid substitutions may be conservative or non-conservative. In embodiments, amino acid substitution(s) may be conservative amino acid substitution(s).

[0018] In embodiments, CD8 polypeptides described herein may be CD8 α or modified CD8 α polypeptides.

[0019] In embodiments, CD8 polypeptides described herein may be CD8 $\alpha\beta$ or modified CD8 α polypeptides.

[0020] In embodiments, a CD8 β polypeptide may comprise the amino acid sequence of any one of SEQ ID NO: 8, 9, 10, 11, 12, 13, or 14.

[0021] In embodiments, a TCR α chain and a TCR β chain may be selected from SEQ ID NO: 15 and 16; 17 and 18; 19 and 20; 21 and 22; 23 and 24; 25 and 26; 27 and 28; 29 and 30; 31 and 32; 33 and 34; 35 and 36; 37 and 38; 39 and 40; 41 and 42; 43 and 44; 45 and 46; 47 and 48; 49 and 50; 51 and 52; 53 and 54; 55 and 56; 57 and 58; 59 and 60; 61 and 62; 63 and 64; 65 and 66; 67 and 68; 69 and 70; 71 and 303; 304 and 74; 75 and 76; 77 and 78; 79 and 80; 81 and 82; 83 and 84; 85 and 86; 87 and 88; 89 and 90; and 91 and 92.

[0022] In embodiments, an isolated nucleic acid may comprise a nucleic acid sequence encoding a T-cell receptor comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain and a β chain. In embodiments, a CD8 polypeptide may comprise a CD8 α chain and/or a CD8 β chain, and the CD8 α chain and/or CD8 β chain may independently be modified or unmodified. An isolated nucleic acid may comprise a nucleic acid at least about 80% identical to the nucleic acid sequence of SEQ ID NO: 267, 269, 271, 273, 275, 277, 279, 281, 283, 285, 287, 289, 291, 295, 297, 299, or 301. An isolated nucleic acid may be at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the nucleic acid sequence of SEQ ID NO: 267, 269, 271, 273, 275, 277, 279, 281, 283, 285, 287, 289, 291, 295, 297, 299, or 301.

[0023] In an aspect, polypeptide sequences and/or nucleic acid sequences described herein may be isolated and/or recombinant sequences.

[0024] In an aspect, cells described herein may be isolated and/or recombinant cells.

[0025] In embodiments, an isolated nucleic acid comprises the nucleic acid sequence of SEQ ID NO: 267.

[0026] In embodiments, an isolated nucleic acid comprises the nucleic acid sequence of SEQ ID NO: 279.

[0027] In embodiments, isolated polypeptide(s) may be encoded by nucleic acids described herein or, due, for example, to codon degeneration, by nucleic acids encoding the same polypeptide.

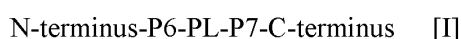
[0028] In embodiments, an isolated polypeptide may comprise an amino acid sequence at least about 80% identical to the amino acid sequence of SEQ ID NO: 268, 270, 272, 274, 276, 278, 280, 282, 284, 286, 288, 290, 292, 296, 298, 300, or 302. An amino acid sequence may be at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 268, 270, 272, 274, 276, 278, 280, 282, 284, 286, 288, 290,

292, 296, 298, 300, or 302. In another aspect, SEQ ID NO: 268, 270, 272, 274, 276, 278, 280, 282, 284, 286, 288, 290, 292, 296, 298, 300, or 302 comprise 1, 2, 3, 4, 5, 10, 15, or 20 or more amino acid substitutions or deletions. In yet another aspect, SEQ ID NO: 268, 270, 272, 274, 276, 278, 280, 282, 284, 286, 288, 290, 292, 296, 298, 300, or 302 comprise at most 1, 2, 3, 4, 5, 10, 15, or 20 amino acid substitutions or deletions.

[0029] In embodiments, an isolated polypeptide may comprise the amino acid sequence of SEQ ID NO: 268.

[0030] In embodiments, an isolated polypeptide may comprise the amino acid sequence of SEQ ID NO: 280.

[0031] In embodiments, a nucleic acid encoding a fusion polypeptide of Formula I:



wherein P6 and P7 are each independently a first and second polypeptides and PL is a linker, wherein PL comprises SEQ ID NO: 387 or 389 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 387 or 389 may be provided.

[0032] In embodiments, a nucleic acid comprising formula II:



wherein N6 and N7 each independently encode a first and second polypeptides and NL encodes a linker, wherein NL comprises SEQ ID NO: 388 or 390 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 388 or 390 may be provided.

[0033] In embodiments, a nucleic acid encoding a polypeptide comprising SEQ ID NO: 309, 311, 313, or 315 or a polypeptide at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 309, 311, 313, or 315 may be provided.

[0034] In embodiments, a nucleic acid encoding a polypeptide comprising SEQ ID NO: 311, 313, or 315 or a polypeptide at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 311, 313, or 315 may be provided.

[0035] In embodiments, a nucleic acid comprising SEQ ID NO: 310, 312, 314, or 316 or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 310, 312, 314, or 316 may be provided.

[0036] In embodiments, a nucleic acid comprising SEQ ID NO: 312, 314, or 316 or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least

about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 312, 314, or 316 may be provided.

[0037] In embodiments, a nucleic acid encoding (i) a polypeptide comprising SEQ ID NO: 307 fused directly or indirectly to an N terminus of a polypeptide comprising any of SEQ ID NO: 309, 311, 313, or 315 or (ii) a polypeptide at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 307 fused directly or indirectly to a polypeptide at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to any of SEQ ID NO: 309, 311, 313, or 315 may be provided.

[0038] In embodiments, a nucleic acid encoding (i) a polypeptide comprising SEQ ID NO: 307 fused directly or indirectly to an N terminus of a polypeptide comprising any of SEQ ID NO: 311, 313, or 315 or (ii) a polypeptide at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 307 fused directly or indirectly to a polypeptide at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to any of SEQ ID NO: 311, 313, or 315 may be provided.

[0039] In embodiments, a nucleic acid may further comprise a nucleic acid encoding a signal peptide directly or indirectly fused to an N terminus of SEQ ID NO: 307 or to an N terminus of a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 307. In embodiments, the signal peptide may be derived from an IgE polypeptide. In embodiments, the signal peptide derived from an IgE polypeptide may comprise SEQ ID NO: 367 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[0040] In embodiments, a nucleic acid comprising (i) SEQ ID NO: 308 fused directly or indirectly to a 5' end of any of SEQ ID NO: 310, 312, 314, or 316 or (ii) a sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 308 fused directly or indirectly to the 5' end of any of a sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to any of SEQ ID NO: 310, 312, 314, or 316 may be provided.

[0041] In embodiments, a nucleic acid comprising (i) SEQ ID NO: 308 fused directly or indirectly to a 5' end of any of SEQ ID NO: 312, 314, or 316 or (ii) a sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 308

fused directly or indirectly to the 5' end of any of a sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to any of SEQ ID NO: 312, 314, or 316 may be provided.

[0042] In embodiments, a nucleic acid may further comprise a nucleic acid encoding a signal peptide directly or indirectly fused to the 5' end of SEQ ID NO: 308 or to 5' end of a sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 308. In embodiments, the signal peptide may be derived from an IgE polypeptide. In embodiments, the signal peptide derived from an IgE polypeptide may comprise SEQ ID NO: 368 or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[0043] In embodiments, a nucleic acid encoding a polypeptide comprising SEQ ID NO: 317, 321, 325, 327, 329, 331, 333, or 335 or a polypeptide at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 317, 321, 325, 327, 329, 331, 333, or 335 may be provided.

[0044] In embodiments, a nucleic acid encoding a polypeptide comprising SEQ ID NO: 317, 321, 325, 327, 329, 331, or 333 or a polypeptide at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 317, 321, 325, 327, 329, 331, or 333 may be provided.

[0045] In embodiments, a nucleic acid may further comprise a nucleic acid encoding a signal peptide directly or indirectly fused to an N terminus of SEQ ID NO: 317, 321, 325, 327, 329, 331, or 333 or to an N terminus of a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 317, 321, 325, 327, 329, 331, or 333. In embodiments, the signal peptide may be derived from an IgE polypeptide. In embodiments, the signal peptide derived from an IgE polypeptide may comprise SEQ ID NO: 367 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[0046] In embodiments, a nucleic acid comprising SEQ ID NO: 318, 322, 326, 328, 330, 332, 334, or 336 or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 318, 322, 326, 328, 330, 332, 334, or 336 may be provided.

[0047] In embodiments, a nucleic acid comprising SEQ ID NO: 318, 322, 326, 328, 330, 332, or 334 or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 318, 322, 326, 328, 330, 332, or 334 may be provided.

[0048] In embodiments, a nucleic acid may further comprise a nucleic acid encoding a signal peptide directly or indirectly fused to the 5' end of SEQ ID NO: 318, 322, 326, 328, 330, 332, or 334 or to 5' end of a sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 318, 322, 326, 328, 330, 332, or 334. In embodiments, the signal peptide may be derived from an IgE polypeptide. In embodiments, the signal peptide derived from an IgE polypeptide may be comprise SEQ ID NO: 368 or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[0049] In embodiments, a nucleic acid encoding a polypeptide comprising SEQ ID NO: 337, 341, 345, 347, 349, 351, 353, or 355 or a polypeptide at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 337, 341, 345, 347, 349, 351, 353, or 355 may be provided.

[0050] In embodiments, a nucleic acid encoding a polypeptide comprising SEQ ID NO: 337, 341, 345, 347, 349, 351, or 353 or a polypeptide at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 337, 341, 345, 347, 349, 351, or 353 may be provided.

[0051] In embodiments, a nucleic acid comprising SEQ ID NO: 338, 342, 346, 348, 350, 352, 354, or 356 or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 338, 342, 346, 348, 350, 352, 354, or 356 may be provided.

[0052] In embodiments, a nucleic acid comprising SEQ ID NO: 338, 342, 346, 348, 350, 352, or 354 or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 338, 342, 346, 348, 350, 352, or 354 may be provided.

[0053] In embodiments, a nucleic acid described herein may further comprise a nucleic acid encoding (a) at least one TCR polypeptide comprising an α chain and a β chain, (b) at least one CD8 polypeptide comprising (i) an α chain, (ii) a β chain, or (iii) both an α chain and a β chain, or (c) at least one TCR polypeptide comprising an α chain and a β chain and at least one CD8 polypeptide comprising (i) an α chain, (ii) a β chain, or (iii) both an α chain and a β chain.

[0054] In embodiments, a polypeptide, polypeptides, or fusion polypeptide encoded by a nucleic acid described herein may be provided.

[0055] In embodiments, a polypeptide or fusion polypeptide comprising an amino acid sequence at least about 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 307, 309, 311, 313, 315, 317, 319, 321, 323, 325, 327, 329, 331, 333, 335, 337, 339, 341, 343, 345, 347, 349, 351, 353, or 355 may be provided.

[0056] In embodiments, a polypeptide or fusion polypeptide comprising an amino acid sequence at least about 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 311, 313, 315, 317, 319, 321, 323, 325, 327, 329, 331, 333, 337, 339, 341, 343, 345, 347, 349, 351, or 353 may be provided.

[0057] In embodiments, a fusion polypeptide comprising a polypeptide at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 307 fused directly or indirectly to an N terminus of any of a polypeptide at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to any of SEQ ID NO: 309, 311, 313, or 315 may be provided.

[0058] In embodiments, a fusion polypeptide comprising a polypeptide at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 307 fused directly or indirectly to an N terminus of any of a polypeptide at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to any of SEQ ID NO: 311, 313, or 315 may be provided.

[0059] In embodiments, a fusion polypeptide may further comprise a signal peptide directly or indirectly fused to an N terminus of a polypeptide at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 307. In embodiments, the signal peptide may be derived from an IgE polypeptide. In embodiments, the signal peptide derived from an IgE polypeptide may comprise SEQ ID NO: 367 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[0060] In embodiments, a nucleic acid comprising: (a) a nucleic acid encoding (i) a T-cell receptor (TCR) comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain and a β chain, or (ii) a TCR comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain without a β chain, and (b) a nucleic acid encoding an IL-15/IL-15R α fusion polypeptide, wherein the TCR α chain and the TCR β chain are selected from SEQ ID NO: 15 and 16, 17 and 18, 19 and 20, 21 and 22, 23 and 24, 25 and 26, 27 and 28, 29 and 30, 31 and 32, 33 and 34, 35 and 36, 37 and 38, 39 and 40, 41 and 42, 43 and 44, 45 and 46, 47 and 48, 49 and 50, 51 and 52, 53 and 54, 55 and 56, 57 and 58, 59 and 60, 61 and 62, 63 and 64, 65 and

66, 67 and 68, 69 and 70, 71 and 303, 304 and 74, 75 and 76, 77 and 78, 79 and 80, 81 and 82, 83 and 84, 85 and 86, 87 and 88, 89 and 90, and 91 and 92; wherein the CD8 α chain is SEQ ID NO: 7, 258, 259, 262, or a variant thereof; wherein, if present, the CD8 β chain is SEQ ID NO: 8, 9, 10, 11, 12, 13, or 14; and wherein the IL-15/IL-15R α fusion polypeptide is selected from (i) SEQ ID NO: 307 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto, directly or indirectly fused to an N terminus of SEQ ID NO: 309 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto, with or without a linker therebetween; (ii) SEQ ID NO: 307 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto, directly or indirectly fused to an N terminus of SEQ ID NO: 311 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto, with or without a linker therebetween; (iii) SEQ ID NO: 307 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto, directly or indirectly fused to an N terminus of SEQ ID NO: 313 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto, with or without a linker therebetween; or (iv) SEQ ID NO: 307 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto, directly or indirectly fused to an N terminus of SEQ ID NO: 315 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto, with or without a linker therebetween may be provided.

[0061] In embodiments, the IL-15/IL-15R α fusion polypeptide may further comprise a signal peptide directly or indirectly fused to the N terminus of SEQ ID NO: 307 of any of (i), (ii), (iii), or (iv) or to the N terminus of a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 307 of any of (i), (ii), (iii), or (iv).

[0062] In embodiments, a nucleic acid comprising: (a) a nucleic acid encoding (i) a T-cell receptor (TCR) comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain and a β chain, or (ii) a TCR comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain without a β chain, and (b) a nucleic acid encoding an IL-15/IL-15R α fusion polypeptide, wherein the TCR α chain and the TCR β chain are selected from SEQ ID NO: 15 and 16, 17 and 18, 19 and 20, 21 and 22, 23 and 24, 25 and 26, 27 and 28, 29 and 30, 31 and 32, 33 and 34, 35 and 36, 37 and 38, 39 and 40, 41 and 42, 43 and 44, 45 and 46, 47 and 48, 49 and 50, 51 and 52, 53 and 54, 55 and 56, 57 and 58, 59 and 60, 61 and 62, 63 and 64, 65 and

66, 67 and 68, 69 and 70, 71 and 303, 304 and 74, 75 and 76, 77 and 78, 79 and 80, 81 and 82, 83 and 84, 85 and 86, 87 and 88, 89 and 90, and 91 and 92; wherein the CD8 α chain is SEQ ID NO: 7, 258, 259, 262, or a variant thereof; wherein, if present, the CD8 β chain is SEQ ID NO: 8, 9, 10, 11, 12, 13, or 14; and wherein the IL-15/IL-15R α fusion polypeptide is selected from (i) SEQ ID NO: 307 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto, directly or indirectly fused to an N terminus of SEQ ID NO: 311 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto, with or without a linker therebetween; (ii) SEQ ID NO: 307 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto, directly or indirectly fused to an N terminus of SEQ ID NO: 313 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto, with or without a linker therebetween; or (iii) SEQ ID NO: 307 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto, directly or indirectly fused to an N terminus of SEQ ID NO: 315 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto, with or without a linker therebetween may be provided.

[0063] In embodiments, the IL-15/IL-15R α fusion polypeptide may further comprise a signal peptide directly or indirectly fused to the N terminus of SEQ ID NO: 307 of any of (i), (ii), or (iii) or to the N terminus of a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 307 of any of (i), (ii), or (iii).

[0064] In embodiments, the signal peptide may be derived from an IgE polypeptide. In embodiments, the signal peptide derived from an IgE polypeptide may comprise SEQ ID NO: 367 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[0065] In embodiments, a nucleic acid comprising: (a) a nucleic acid encoding (i) a T-cell receptor (TCR) comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain and a β chain, or (ii) a TCR comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain without a β chain, and (b) a nucleic acid encoding an IL-15/IL-15R α fusion polypeptide, wherein the TCR α chain and the TCR β chain are selected from SEQ ID NO: 15 and 16, 17 and 18, 19 and 20, 21 and 22, 23 and 24, 25 and 26, 27 and 28, 29 and 30, 31 and 32, 33 and 34, 35 and 36, 37 and 38, 39 and 40, 41 and 42, 43 and 44, 45 and 46, 47 and 48, 49 and 50, 51 and 52, 53 and 54, 55 and 56, 57 and 58, 59 and 60, 61 and 62, 63 and 64, 65 and

66, 67 and 68, 69 and 70, 71 and 303, 304 and 74, 75 and 76, 77 and 78, 79 and 80, 81 and 82, 83 and 84, 85 and 86, 87 and 88, 89 and 90, and 91 and 92; wherein the CD8 α chain is SEQ ID NO: 7, 258, 259, 262, or a variant thereof; wherein, if present, the CD8 β chain is SEQ ID NO: 8, 9, 10, 11, 12, 13, or 14; and wherein the IL-15/IL-15R α fusion polypeptide is selected from SEQ ID NO: 317, 319, 321, 323, 325, 327, 329, 331, 333, or 335, or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 317, 319, 321, 323, 325, 327, 329, 331, 333, or 335 may be provided.

[0066] In embodiments, the IL-15/IL-15R α fusion polypeptide may further comprise a signal peptide directly or indirectly fused to an N terminus of SEQ ID NO: 317, 319, 321, 323, 325, 327, 329, 331, 333, or 335, or directly or indirectly fused to an N terminus of a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 317, 319, 321, 323, 325, 327, 329, 331, 333, or 335.

[0067] In embodiments, a nucleic acid comprising: (a) a nucleic acid encoding (i) a T-cell receptor (TCR) comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain and a β chain, or (ii) a TCR comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain without a β chain, and (b) a nucleic acid encoding an IL-15/IL-15R α fusion polypeptide, wherein the TCR α chain and the TCR β chain are selected from SEQ ID NO: 15 and 16, 17 and 18, 19 and 20, 21 and 22, 23 and 24, 25 and 26, 27 and 28, 29 and 30, 31 and 32, 33 and 34, 35 and 36, 37 and 38, 39 and 40, 41 and 42, 43 and 44, 45 and 46, 47 and 48, 49 and 50, 51 and 52, 53 and 54, 55 and 56, 57 and 58, 59 and 60, 61 and 62, 63 and 64, 65 and 66, 67 and 68, 69 and 70, 71 and 303, 304 and 74, 75 and 76, 77 and 78, 79 and 80, 81 and 82, 83 and 84, 85 and 86, 87 and 88, 89 and 90, and 91 and 92; wherein the CD8 α chain is SEQ ID NO: 7, 258, 259, 262, or a variant thereof; wherein, if present, the CD8 β chain is SEQ ID NO: 8, 9, 10, 11, 12, 13, or 14; and wherein the IL-15/IL-15R α fusion polypeptide is selected from SEQ ID NO: 317, 319, 321, 323, 325, 327, 329, 331, or 333, or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 317, 319, 321, 323, 325, 327, 329, 331, or 333 may be provided.

[0068] In embodiments, the IL-15/IL-15R α fusion polypeptide may further comprise a signal peptide directly or indirectly fused to an N terminus of SEQ ID NO: 317, 319, 321, 323, 325, 327, 329, 331, or 333, or directly or indirectly fused to an N terminus of a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 317, 319, 321, 323, 325, 327, 329, 331, or 333.

[0069] In embodiments, the signal peptide may be derived from an IgE polypeptide. In embodiments, the signal peptide derived from an IgE polypeptide may comprise SEQ ID NO:

367 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[0070] In embodiments, a nucleic acid comprising: (a) a nucleic acid encoding (i) a T-cell receptor (TCR) comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain and a β chain, or (ii) a TCR comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain without a β chain, and (b) a nucleic acid encoding a fusion polypeptide comprising (i) SEQ ID NO: 367 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 367 fused to (ii) an N terminus of an IL-15/IL-15R α fusion polypeptide, wherein the TCR α chain and the TCR β chain are selected from SEQ ID NO: 15 and 16, 17 and 18, 19 and 20, 21 and 22, 23 and 24, 25 and 26, 27 and 28, 29 and 30, 31 and 32, 33 and 34, 35 and 36, 37 and 38, 39 and 40, 41 and 42, 43 and 44, 45 and 46, 47 and 48, 49 and 50, 51 and 52, 53 and 54, 55 and 56, 57 and 58, 59 and 60, 61 and 62, 63 and 64, 65 and 66, 67 and 68, 69 and 70, 71 and 303, 304 and 74, 75 and 76, 77 and 78, 79 and 80, 81 and 82, 83 and 84, 85 and 86, 87 and 88, 89 and 90, and 91 and 92; wherein the CD8 α chain is SEQ ID NO: 7, 258, 259, 262, or a variant thereof; wherein, if present, the CD8 β chain is SEQ ID NO: 8, 9, 10, 11, 12, 13, or 14; and wherein the nucleic acid of (b) encodes a fusion polypeptide selected from SEQ ID NO: 337, 339, 341, 343, 345, 347, 349, 351, 353, or 355, or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 337, 339, 341, 343, 345, 347, 349, 351, 353, or 355 may be provided.

[0071] In embodiments, a nucleic acid comprising: (a) a nucleic acid encoding (i) a T-cell receptor (TCR) comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain and a β chain, or (ii) a TCR comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain without a β chain, and (b) a nucleic acid encoding a fusion polypeptide comprising (i) SEQ ID NO: 367 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 367 fused to (ii) an N terminus of an IL-15/IL-15R α fusion polypeptide, wherein the TCR α chain and the TCR β chain are selected from SEQ ID NO: 15 and 16, 17 and 18, 19 and 20, 21 and 22, 23 and 24, 25 and 26, 27 and 28, 29 and 30, 31 and 32, 33 and 34, 35 and 36, 37 and 38, 39 and 40, 41 and 42, 43 and 44, 45 and 46, 47 and 48, 49 and 50, 51 and 52, 53 and 54, 55 and 56, 57 and 58, 59 and 60, 61 and 62, 63 and 64, 65 and 66, 67 and 68, 69 and 70, 71 and 303, 304 and 74, 75 and 76, 77 and 78, 79 and 80, 81 and 82, 83 and 84, 85 and 86, 87 and 88, 89 and 90, and 91 and 92; wherein the CD8 α chain is SEQ ID NO: 7, 258, 259, 262, or a variant thereof; wherein, if present, the CD8 β chain is SEQ ID NO: 8, 9, 10, 11, 12, 13, or 14; and wherein the nucleic acid of (b) encodes a fusion polypeptide selected from SEQ ID NO: 337, 339, 341, 343,

345, 347, 349, 351, or 353, or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 337, 339, 341, 343, 345, 347, 349, 351, or 353 may be provided.

[0072] In embodiments, a nucleic acid comprising: (a) a nucleic acid encoding (i) a T-cell receptor (TCR) comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain and a β chain, or (ii) a TCR comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain without a β chain, and (b) a nucleic acid encoding an IL-15/IL-15R α fusion polypeptide, wherein the TCR α chain and the TCR β chain are selected from SEQ ID NO: 15 and 16, 17 and 18, 19 and 20, 21 and 22, 23 and 24, 25 and 26, 27 and 28, 29 and 30, 31 and 32, 33 and 34, 35 and 36, 37 and 38, 39 and 40, 41 and 42, 43 and 44, 45 and 46, 47 and 48, 49 and 50, 51 and 52, 53 and 54, 55 and 56, 57 and 58, 59 and 60, 61 and 62, 63 and 64, 65 and 66, 67 and 68, 69 and 70, 71 and 303, 304 and 74, 75 and 76, 77 and 78, 79 and 80, 81 and 82, 83 and 84, 85 and 86, 87 and 88, 89 and 90, and 91 and 92; wherein the CD8 α chain is SEQ ID NO: 7, 258, 259, 262, or a variant thereof; wherein, if present, the CD8 β chain is SEQ ID NO: 8, 9, 10, 11, 12, 13, or 14; and wherein the IL-15/IL-15R α fusion polypeptide is selected from SEQ ID NO: 317, 321, 325, 327, 329, 331, 333, or 335 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 317, 321, 325, 327, 329, 331, 333, or 335 may be provided.

[0073] In embodiments, the IL-15/IL-15R α fusion polypeptide may further comprise a signal peptide directly or indirectly fused to an N terminus of SEQ ID NO: 317, 321, 325, 327, 329, 331, 333, or 335, or to an N terminus of a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 317, 321, 325, 327, 329, 331, 333, or 335.

[0074] In embodiments, a nucleic acid comprising: (a) a nucleic acid encoding (i) a T-cell receptor (TCR) comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain and a β chain, or (ii) a TCR comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain without a β chain, and (b) a nucleic acid encoding an IL-15/IL-15R α fusion polypeptide, wherein the TCR α chain and the TCR β chain are selected from SEQ ID NO: 15 and 16, 17 and 18, 19 and 20, 21 and 22, 23 and 24, 25 and 26, 27 and 28, 29 and 30, 31 and 32, 33 and 34, 35 and 36, 37 and 38, 39 and 40, 41 and 42, 43 and 44, 45 and 46, 47 and 48, 49 and 50, 51 and 52, 53 and 54, 55 and 56, 57 and 58, 59 and 60, 61 and 62, 63 and 64, 65 and 66, 67 and 68, 69 and 70, 71 and 303, 304 and 74, 75 and 76, 77 and 78, 79 and 80, 81 and 82, 83 and 84, 85 and 86, 87 and 88, 89 and 90, and 91 and 92; wherein the CD8 α chain is SEQ ID NO: 7, 258, 259, 262, or a variant thereof; wherein, if present, the CD8 β chain is SEQ ID NO: 8, 9, 10, 11, 12, 13, or 14; and wherein the IL-15/IL-15R α fusion polypeptide is selected from SEQ

ID NO: 317, 321, 325, 327, 329, 331, or 333 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 317, 321, 325, 327, 329, 331, or 333 may be provided.

[0075] In embodiments, the IL-15/IL-15R α fusion polypeptide may further comprise a signal peptide directly or indirectly fused to an N terminus of SEQ ID NO: 317, 321, 325, 327, 329, 331, or 333, or to an N terminus of a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 317, 321, 325, 327, 329, 331, or 333.

[0076] In embodiments, the signal peptide may be derived from an IgE polypeptide. In embodiments, the signal peptide derived from an IgE polypeptide may comprise SEQ ID NO: 367 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[0077] In embodiments, a nucleic acid comprising: (a) a nucleic acid encoding (i) a T-cell receptor (TCR) comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain and a β chain, or (ii) a TCR comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain without a β chain, and (b) a nucleic acid encoding a fusion polypeptide comprising (i) SEQ ID NO: 367 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 367 fused to (ii) an N terminus of an IL-15/IL-15R α fusion polypeptide, wherein the TCR α chain and the TCR β chain are selected from SEQ ID NO: 15 and 16, 17 and 18, 19 and 20, 21 and 22, 23 and 24, 25 and 26, 27 and 28, 29 and 30, 31 and 32, 33 and 34, 35 and 36, 37 and 38, 39 and 40, 41 and 42, 43 and 44, 45 and 46, 47 and 48, 49 and 50, 51 and 52, 53 and 54, 55 and 56, 57 and 58, 59 and 60, 61 and 62, 63 and 64, 65 and 66, 67 and 68, 69 and 70, 71 and 303, 304 and 74, 75 and 76, 77 and 78, 79 and 80, 81 and 82, 83 and 84, 85 and 86, 87 and 88, 89 and 90, and 91 and 92; wherein the CD8 α chain is SEQ ID NO: 7, 258, 259, 262, or a variant thereof; wherein, if present, the CD8 β chain is SEQ ID NO: 8, 9, 10, 11, 12, 13, or 14; and wherein the nucleic acid of (b) encodes a fusion polypeptide selected from SEQ ID NO: 337, 339, 341, 343, 345, 347, 349, 351, 353, or 355 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 337, 339, 341, 345, 347, 349, 351, 353, or 355 may be provided.

[0078] In embodiments, a nucleic acid comprising: (a) a nucleic acid encoding (i) a T-cell receptor (TCR) comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain and a β chain, or (ii) a TCR comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain without a β chain, and (b) a nucleic acid encoding a fusion polypeptide comprising (i) SEQ ID NO: 367 or a sequence at least about 95%, at least about 96%, at least

about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 367 fused to (ii) an N terminus of an IL-15/IL-15R α fusion polypeptide, wherein the TCR α chain and the TCR β chain are selected from SEQ ID NO: 15 and 16, 17 and 18, 19 and 20, 21 and 22, 23 and 24, 25 and 26, 27 and 28, 29 and 30, 31 and 32, 33 and 34, 35 and 36, 37 and 38, 39 and 40, 41 and 42, 43 and 44, 45 and 46, 47 and 48, 49 and 50, 51 and 52, 53 and 54, 55 and 56, 57 and 58, 59 and 60, 61 and 62, 63 and 64, 65 and 66, 67 and 68, 69 and 70, 71 and 303, 304 and 74, 75 and 76, 77 and 78, 79 and 80, 81 and 82, 83 and 84, 85 and 86, 87 and 88, 89 and 90, and 91 and 92; wherein the CD8 α chain is SEQ ID NO: 7, 258, 259, 262, or a variant thereof; wherein, if present, the CD8 β chain is SEQ ID NO: 8, 9, 10, 11, 12, 13, or 14; and wherein the nucleic acid of (b) encodes a fusion polypeptide selected from SEQ ID NO: 337, 341, 345, 347, 349, 351, or 353 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 337, 341, 345, 347, 349, 351, or 353 may be provided.

[0079] In embodiments, a nucleic acid comprising: (a) a nucleic acid encoding (i) a T-cell receptor (TCR) comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain and a β chain, or (ii) a TCR comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain without a β chain, and (b) a nucleic acid encoding an IL-15/IL-15R α fusion polypeptide, wherein the TCR α chain and the TCR β chain are selected from SEQ ID NO: 15 and 16, 57 and 58, 59 and 60, 61 and 62, 63 and 64, 65 and 66, 67 and 68, 69 and 70, and 71 and 303; wherein the CD8 α chain is SEQ ID NO: 7, 258, 259, 262, or a variant thereof; and wherein, if present, the CD8 β chain is SEQ ID NO: 8, 9, 10, 11, 12, 13, or 14 may be provided.

[0080] In embodiments, the IL-15/IL-15R α fusion polypeptide may comprise SEQ ID NO: 317 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[0081] In embodiments, the IL-15/IL-15R α fusion polypeptide may comprise SEQ ID NO: 319 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[0082] In embodiments, the IL-15/IL-15R α fusion polypeptide may comprise SEQ ID NO: 321 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[0083] In embodiments, the IL-15/IL-15R α fusion polypeptide may comprise SEQ ID NO: 323 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[0084] In embodiments, the IL-15/IL-15R α fusion polypeptide may comprise SEQ ID NO: 325 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[0085] In embodiments, the IL-15/IL-15R α fusion polypeptide may comprise SEQ ID NO: 327 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[0086] In embodiments, the IL-15/IL-15R α fusion polypeptide may comprise SEQ ID NO: 329 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[0087] In embodiments, the IL-15/IL-15R α fusion polypeptide may comprise SEQ ID NO: 331 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[0088] In embodiments, the IL-15/IL-15R α fusion polypeptide may comprise SEQ ID NO: 333 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[0089] In embodiments, the IL-15/IL-15R α fusion polypeptide may comprise SEQ ID NO: 335 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[0090] In embodiments, the IL-15/IL-15R α fusion polypeptide may further comprise a signal peptide directly or indirectly fused to an N terminus of the IL-15/IL-15R α fusion polypeptide. In embodiments, the signal peptide may be derived from an IgE polypeptide. In embodiments, the signal peptide derived from an IgE polypeptide may comprise SEQ ID NO: 367 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[0091] In embodiments, a nucleic acid comprising: (a) a nucleic acid encoding (i) a T-cell receptor (TCR) comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain and a β chain, or (ii) a TCR comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain without a β chain, and (b) a nucleic acid encoding a fusion polypeptide comprising (i) SEQ ID NO: 367 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 367 fused to (ii) an N terminus of an IL-15/IL-15R α fusion polypeptide, wherein the TCR α chain and the TCR β chain are selected from SEQ ID NO: 15 and 16, 57 and 58, 59 and 60, 61 and 62, 63 and 64, 65 and 66, 67 and 68, 69 and 70, and 71 and 303; wherein the CD8 α chain is SEQ ID NO: 7, 258, 259, 262, or a variant thereof; and wherein, if present, the CD8 β chain is SEQ ID NO: 8, 9, 10, 11, 12, 13, or 14 may be provided.

[0092] In embodiments, the nucleic acid of (b) may encode SEQ ID NO: 337, 339, 341, 343, 345, 347, 349, 351, 353 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to any of the aforementioned SEQ ID NOs.

[0093] In embodiments, a nucleic acid comprising: (a) a nucleic acid at least about 80% identical to the nucleic acid of SEQ ID NO: 267, 269, 271, 273, 275, 277, 279, 281, 283, 285, 287, 289, 291, 295, 297, 299, or 301 and (b) a nucleic acid encoding an IL-15/IL-15R α fusion polypeptide may be provided.

[0094] In embodiments, a nucleic acid comprising: (a) a nucleic acid at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the nucleic acid of SEQ ID NO: 267, 269, 271, 273, 275, 277, 279, 281, 283, 285, 287, 289, 291, 295, 297, 299, or 301 and (b) a nucleic acid encoding an IL-15/IL-15R α fusion polypeptide may be provided.

[0095] In embodiments, the nucleic acid encoding an IL-15/IL-15R α fusion polypeptide may be selected from (i) SEQ ID NO: 308 or a sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical thereto, directly or indirectly fused to a 5' end of SEQ ID NO: 310 or a sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical thereto, with or without a nucleic acid encoding a linker therebetween; (ii) SEQ ID NO: 308 or a sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical thereto, directly or indirectly fused to a 5' end of SEQ ID NO: 312 or a sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical thereto, with or without a nucleic acid encoding a linker therebetween; (iii) SEQ ID NO: 308 or a sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical thereto, directly or indirectly fused to a 5' end of SEQ ID NO: 314 or a sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical thereto, with or without a nucleic acid encoding a linker therebetween; or (iv) SEQ ID NO: 308 or a sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical thereto, directly or indirectly fused to a 5' end of SEQ ID NO: 316 or a sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical thereto, with or without a nucleic acid encoding a linker therebetween.

[0096] In embodiments, a nucleic acid may further comprise a nucleic acid encoding a signal peptide, wherein the nucleic acid encoding the signal peptide is directly or indirectly fused to the 5' end of SEQ ID NO: 308 of any of (i), (ii), (iii), or (iv) or to the 5' end of sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 308 of any of (i), (ii), (iii), or (iv).

[0097] In embodiments, the nucleic acid encoding an IL-15/IL-15R α fusion polypeptide may be selected from (i) SEQ ID NO: 308 or a sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical thereto, directly or indirectly fused to a 5' end of SEQ ID NO: 312 or a sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical thereto, with or without a nucleic acid encoding a linker therebetween; (ii) SEQ ID NO: 308 or a sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical thereto, directly or indirectly fused to a 5' end of SEQ ID NO: 314 or a sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical thereto, with or without a nucleic acid encoding a linker therebetween; or (iii) SEQ ID NO: 308 or a sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical thereto, directly or indirectly fused to a 5' end of SEQ ID NO: 316 or a sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical thereto, with or without a nucleic acid encoding a linker therebetween.

[0098] In embodiments, a nucleic acid may further comprise a nucleic acid encoding a signal peptide, wherein the nucleic acid encoding the signal peptide is directly or indirectly fused to the 5' end of SEQ ID NO: 308 of any of (i), (ii), or (iii) or to the 5' end of sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 308 of any of (i), (ii), or (iii).

[0099] In embodiments, the signal peptide may be derived from an IgE polypeptide. In embodiments, the nucleic acid encoding the signal peptide may comprise SEQ ID NO: 368 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[00100] In embodiments, the nucleic acid encoding an IL-15/IL-15R α fusion polypeptide may be selected from SEQ ID NO: 318, 320, 322, 324, 326, 328, 330, 332, 334, or 336 or a sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the nucleic acid of SEQ ID NO: 318, 320, 322, 324, 326, 328, 330, 332, 334, or 336.

[00101] In embodiments, the nucleic acid encoding an IL-15/IL-15R α fusion polypeptide may further comprise a nucleic acid encoding a signal peptide, wherein the nucleic acid encoding the signal peptide is directly or indirectly fused to a 5' end of SEQ ID NO: 318, 320, 322, 324, 326, 328, 330, 332, 334, or 336 or a sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the nucleic acid of SEQ ID NO: 318, 320, 322, 324, 326, 328, 330, 332, 334, or 336.

[00102] In embodiments, the nucleic acid encoding an IL-15/IL-15R α fusion polypeptide may be selected from SEQ ID NO: 318, 320, 322, 324, 326, 328, 330, 332, or 334 or a sequence at

least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the nucleic acid of SEQ ID NO: 318, 320, 322, 324, 326, 328, 330, 332, or 334.

[00103] In embodiments, the nucleic acid encoding an IL-15/IL-15R α fusion polypeptide may further comprise a nucleic acid encoding a signal peptide, wherein the nucleic acid encoding the signal peptide is directly or indirectly fused to a 5' end of SEQ ID NO: 318, 320, 322, 324, 326, 328, 330, 332, or 334 or a sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the nucleic acid of SEQ ID NO: 318, 320, 322, 324, 326, 328, 330, 332, or 334.

[00104] In embodiments, the signal peptide may be derived from an IgE polypeptide. In embodiments, the nucleic acid encoding the signal peptide may comprise SEQ ID NO: 368 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[00105] In embodiments, the nucleic acid encoding an IL-15/IL-15R α fusion polypeptide (i) may further comprise a nucleic acid encoding a signal peptide derived from an IgE polypeptide and (ii) may be selected from SEQ ID NO: 338, 340, 342, 344, 346, 348, 350, 352, 354, or 356 or a sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the nucleic acid of SEQ ID NO: 338, 340, 342, 344, 346, 348, 350, 352, 354, or 356.

[00106] In embodiments, the nucleic acid encoding an IL-15/IL-15R α fusion polypeptide (i) may further comprise a nucleic acid encoding a signal peptide derived from an IgE polypeptide and (ii) may be selected from SEQ ID NO: 338, 340, 342, 344, 346, 348, 350, 352, or 354 or a sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the nucleic acid of SEQ ID NO: 338, 340, 342, 344, 346, 348, 350, 352, or 354.

[00107] In embodiments, the nucleic acid encoding an IL-15/IL-15R α fusion polypeptide may be selected from SEQ ID NO: 318, 322, 326, 328, 330, 332, 334, or 336 or a sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the nucleic acid of SEQ ID NO: 318, 322, 326, 328, 330, 332, 334, or 336.

[00108] In embodiments, the nucleic acid encoding an IL-15/IL-15R α fusion polypeptide may further comprise a nucleic acid encoding a signal peptide, wherein the nucleic acid encoding the signal peptide is directly or indirectly fused to a 5' end of SEQ ID NO: 318, 322, 326, 328, 330, 332, 334, or 336 or a sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the nucleic acid of SEQ ID NO: 318, 322, 326, 328, 330, 332, 334, or 336.

[00109] In embodiments, the nucleic acid encoding an IL-15/IL-15R α fusion polypeptide may be selected from SEQ ID NO: 318, 322, 326, 328, 330, 332, or 334 or a sequence at least about

90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the nucleic acid of SEQ ID NO: 318, 322, 326, 328, 330, 332, or 334.

[00110] In embodiments, the nucleic acid encoding an IL-15/IL-15R α fusion polypeptide may further comprise a nucleic acid encoding a signal peptide, wherein the nucleic acid encoding the signal peptide is directly or indirectly fused to a 5' end of SEQ ID NO: 318, 322, 326, 328, 330, 332, or 334 or a sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the nucleic acid of SEQ ID NO: 318, 322, 326, 328, 330, 332, or 334.

[00111] In embodiments, the signal peptide may be derived from an IgE polypeptide. In embodiments, the nucleic acid encoding the signal peptide may comprise SEQ ID NO: 368 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

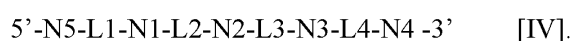
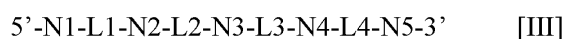
[00112] In embodiments, the nucleic acid encoding an IL-15/IL-15R α fusion polypeptide (i) may further comprise a nucleic acid encoding a signal peptide derived from an IgE polypeptide and (ii) may be selected from SEQ ID NO: 338, 342, 346, 348, 350, 352, 354, or 356 or a sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the nucleic acid of SEQ ID NO: 338, 342, 346, 348, 350, 352, 354, or 356.

[00113] In embodiments, the nucleic acid encoding an IL-15/IL-15R α fusion polypeptide (i) may further comprise a nucleic acid encoding a signal peptide derived from an IgE polypeptide and (ii) may be selected from SEQ ID NO: 338, 342, 346, 348, 350, 352, or 354 or a sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the nucleic acid of SEQ ID NO: 338, 342, 346, 348, 350, 352, or 354.

[00114] In embodiments, a vector comprising a nucleic acid encoding at least one CD8 α chain, at least one TCR α chain, at least one TCR β chain, at least one IL-15/IL-15R α fusion polypeptide, and optionally at least one CD8 β chain may be provided.

[00115] In embodiments, a vector comprising N1, N2, N3, N4, N5, L1, L2, L3, and L4, in any order, wherein N1 comprises a nucleic acid encoding a CD8 β chain and is present or absent, N2 comprises a nucleic acid encoding a CD8 α chain, N3 comprises a nucleic acid encoding a TCR β chain, N4 comprises a nucleic acid encoding a TCR α chain, and N5 comprises a nucleic acid encoding an IL-15/IL-15R α fusion polypeptide; and wherein L1-L4 each comprises a nucleic acid encoding at least one linker, wherein each of L1-L4 is independently the same or different, and wherein each of L1-L4 is independently present or absent may be provided.

[00116] In embodiments, a vector may comprise Formula III or Formula IV:



[00117] In embodiments, N1 may comprise a nucleic acid encoding SEQ ID NO: 8, 9, 10, 11, 12, 13, or 14.

[00118] In embodiments, N2 comprises a nucleic acid encoding a SEQ ID NO: 7, 258, 259, 262, or a variant thereof.

[00119] In embodiments, N4 and N3 may comprise nucleic acids encoding SEQ ID NO: 15 and 16, 17 and 18, 19 and 20, 21 and 22, 23 and 24, 25 and 26, 27 and 28, 29 and 30, 31 and 32, 33 and 34, 35 and 36, 37 and 38, 39 and 40, 41 and 42, 43 and 44, 45 and 46, 47 and 48, 49 and 50, 51 and 52, 53 and 54, 55 and 56, 57 and 58, 59 and 60, 61 and 62, 63 and 64, 65 and 66, 67 and 68, 69 and 70, 71 and 303, 304 and 74, 75 and 76, 77 and 78, 79 and 80, 81 and 82, 83 and 84, 85 and 86, 87 and 88, 89 and 90, or 91 and 92.

[00120] In embodiments, N5 may comprise a nucleic acid encoding (i) SEQ ID NO: 307 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 307, directly or indirectly fused to an N terminus of SEQ ID NO: 309 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 309, with or without a linker therebetween; (ii) SEQ ID NO: 307 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 307, directly or indirectly fused to an N terminus of SEQ ID NO: 311 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 311, with or without a linker therebetween; (iii) SEQ ID NO: 307 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 307, directly or indirectly fused to an N terminus of SEQ ID NO: 313 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 313, with or without a linker therebetween; or (iv) SEQ ID NO: 307 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 307, directly or indirectly fused to an N terminus of SEQ ID NO: 315 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 315, with or without a linker therebetween.

[00121] In embodiments, N5 may further comprise a nucleic acid encoding a signal peptide directly or indirectly fused to the 5' end of the nucleic acid encoding SEQ ID NO: 307 of any of (i), (ii), (iii), or (iv) or to the 5' end of the nucleic acid encoding the sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 307 of any of (i), (ii), (iii), or (iv).

[00122] In embodiments, N5 may comprise a nucleic acid encoding (i) SEQ ID NO: 307 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 307, directly or indirectly fused to an N terminus of SEQ ID NO: 311 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 311, with or without a linker therebetween; (ii) SEQ ID NO: 307 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 307, directly or indirectly fused to an N terminus of SEQ ID NO: 313 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 313, with or without a linker therebetween; or (iii) SEQ ID NO: 307 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 307, directly or indirectly fused to an N terminus of SEQ ID NO: 315 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 315, with or without a linker therebetween.

[00123] In embodiments, N5 may further comprise a nucleic acid encoding a signal peptide directly or indirectly fused to the 5' end of the nucleic acid encoding SEQ ID NO: 307 of any of (i), (ii), or (iii) or to the 5' end of the nucleic acid encoding the sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 307 of any of (i), (ii), or (iii).

[00124] In embodiments, the signal peptide may be derived from an IgE polypeptide. In embodiments, the signal peptide derived from an IgE polypeptide may comprise SEQ ID NO: 367 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[00125] In embodiments, N5 may comprise a nucleic acid encoding SEQ ID NO: 317, 319, 321, 323, 325, 327, 329, 331, 333, or 335 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 317, 319, 321, 323, 325, 327, 329, 331, 333, or 335.

[00126] In embodiments, N5 may further comprise a nucleic acid encoding a signal peptide directly or indirectly fused to the 5' end of the nucleic acid encoding SEQ ID NO: 317, 319, 321, 323, 325, 327, 329, 331, 333, or 335 or to the 5' end of the nucleic acid encoding the sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 317, 319, 321, 323, 325, 327, 329, 331, 333, or 335.

[00127] In embodiments, N5 may comprise a nucleic acid encoding SEQ ID NO: 317, 319, 321, 323, 325, 327, 329, 331, or 333 or a sequence at least about 95%, at least about 96%, at

least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 317, 319, 321, 323, 325, 327, 329, 331, or 333.

[00128] In embodiments, N5 may further comprise a nucleic acid encoding a signal peptide directly or indirectly fused to the 5' end of the nucleic acid encoding SEQ ID NO: 317, 319, 321, 323, 325, 327, 329, 331, or 333 or to the 5' end of the nucleic acid encoding the sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 317, 319, 321, 323, 325, 327, 329, 331, or 333.

[00129] In embodiments, the signal peptide may be derived from an IgE polypeptide. In embodiments, the signal peptide derived from an IgE polypeptide may comprise SEQ ID NO: 367 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[00130] In embodiments, (i) N5 may further comprise a nucleic acid encoding a signal peptide derived from an IgE polypeptide and (ii) N5 may encode SEQ ID NO: 337, 339, 341, 343, 345, 347, 349, 351, 353, or 355, or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 337, 339, 341, 343, 345, 347, 349, 351, 353, or 355.

[00131] In embodiments, (i) N5 may further comprise a nucleic acid encoding a signal peptide derived from an IgE polypeptide and (ii) N5 may encode SEQ ID NO: 337, 339, 341, 343, 345, 347, 349, 351, or 353, or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 337, 339, 341, 343, 345, 347, 349, 351, or 353.

[00132] In embodiments, N5 may comprise a nucleic acid encoding SEQ ID NO: 317, 321, 325, 327, 329, 331, 333, or 335 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 317, 321, 325, 327, 329, 331, 333, or 335.

[00133] In embodiments, N5 may further comprise a nucleic acid encoding a signal peptide directly or indirectly fused to the 5' end of the nucleic acid encoding SEQ ID NO: 317, 321, 325, 327, 329, 331, 333, or 335 or to the 5' end of the nucleic acid encoding the sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 317, 321, 325, 327, 329, 331, 333, or 335.

[00134] In embodiments, N5 may comprise a nucleic acid encoding SEQ ID NO: 317, 321, 325, 327, 329, 331, or 333 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 317, 321, 325, 327, 329, 331, or 333.

[00135] In embodiments, N5 may further comprise a nucleic acid encoding a signal peptide directly or indirectly fused to the 5' end of the nucleic acid encoding SEQ ID NO: 317, 321, 325, 327, 329, 331, or 333 or to the 5' end of the nucleic acid encoding the sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 317, 321, 325, 327, 329, 331, or 333.

[00136] In embodiments, the signal peptide may be derived from an IgE polypeptide. In embodiments, the signal peptide derived from an IgE polypeptide may comprise SEQ ID NO: 367 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[00137] In embodiments, (i) N5 may further comprise a nucleic acid encoding a signal peptide derived from an IgE polypeptide and (ii) N5 may encode SEQ ID NO: 337, 341, 345, 347, 349, 351, or 353 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 337, 341, 345, 347, 349, 351, or 353.

[00138] In embodiments, (i) the vector may further encode a 2A peptide or an internal ribosome entry site (IRES) positioned between N1 and L1, between L1 and N2, between N2 and L2, between L2 and N3, between N3 and L3, between L3 and N4, between N4 and L4, between L4 and N5, or any combination thereof or (ii) the vector may further encode a 2A peptide or an internal ribosome entry site (IRES) positioned between N5 and L1, between L1 and N1, between N1 and L2, between L2 and N2, between N2 and L3, between L3 and N3, between N3 and L4, between L4 and N4, or any combination thereof.

[00139] In embodiments, (i) the vector may further encode a furin positioned between N1 and L1, between L1 and N2, between N2 and L2, between L2 and N3, between N3 and L3, between L3 and N4, between N4 and L4, between L4 and N5, or any combination thereof or (ii) the vector may further encode a furin positioned between N5 and L1, between L1 and N1, between N1 and L2, between L2 and N2, between N2 and L3, between L3 and N3, between N3 and L4, between L4 and N4, or any combination thereof.

[00140] In embodiments, the 2A peptide may be P2A (SEQ ID NO: 93), T2A (SEQ ID NO: 94), E2A (SEQ ID NO: 95), or F2A (SEQ ID NO: 96).

[00141] In embodiments, the IRES may be selected from the group consisting of IRES from picornavirus, IRES from flavivirus, IRES from pestivirus, IRES from retrovirus, IRES from lentivirus, IRES from insect RNA virus, and IRES from cellular mRNA.

[00142] In embodiments, a T cell and/or natural killer cell comprising: (a) (i) a T-cell receptor (TCR) comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain and a β chain, or (ii) a TCR comprising an α chain and a β chain and a CD8 polypeptide comprising an

α chain without a β chain, and (b) an IL-15/IL-15R α fusion polypeptide, wherein the TCR α chain and the TCR β chain are selected from SEQ ID NO: 15 and 16, 17 and 18, 19 and 20, 21 and 22, 23 and 24, 25 and 26, 27 and 28, 29 and 30, 31 and 32, 33 and 34, 35 and 36, 37 and 38, 39 and 40, 41 and 42, 43 and 44, 45 and 46, 47 and 48, 49 and 50, 51 and 52, 53 and 54, 55 and 56, 57 and 58, 59 and 60, 61 and 62, 63 and 64, 65 and 66, 67 and 68, 69 and 70, 71 and 303, 304 and 74, 75 and 76, 77 and 78, 79 and 80, 81 and 82, 83 and 84, 85 and 86, 87 and 88, 89 and 90, and 91 and 92; wherein the CD8 α chain is SEQ ID NO: 7, 258, 259, 262, or a variant thereof; wherein, if present, the CD8 β chain is SEQ ID NO: 8, 9, 10, 11, 12, 13, or 14; and wherein the IL-15/IL-15R α fusion polypeptide is selected from (i) SEQ ID NO: 307 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 307, directly or indirectly fused to an N terminus of SEQ ID NO: 309 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 309, with or without a linker therebetween; (ii) SEQ ID NO: 307 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 307, directly or indirectly fused to an N terminus of SEQ ID NO: 311 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 311, with or without a linker therebetween; (iii) SEQ ID NO: 307 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 307, directly or indirectly fused to an N terminus of SEQ ID NO: 313 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 313, with or without a linker therebetween; or (iv) SEQ ID NO: 307 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 307, directly or indirectly fused to an N terminus of SEQ ID NO: 315 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 315, with or without a linker therebetween may be provided.

[00143] In embodiments, the IL-15/IL-15R α fusion polypeptide may further comprise a signal peptide directly or indirectly fused to the N terminus of SEQ ID NO: 307 of any of (i), (ii), (iii), or (iv) or to the N terminus of a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 307 of any of (i), (ii), (iii), or (iv).

[00144] In embodiments, a T cell and/or natural killer cell comprising: (a) (i) a T-cell receptor (TCR) comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain and a

β chain, or (ii) a TCR comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain without a β chain, and (b) an IL-15/IL-15R α fusion polypeptide, wherein the TCR α chain and the TCR β chain are selected from SEQ ID NO: 15 and 16, 17 and 18, 19 and 20, 21 and 22, 23 and 24, 25 and 26, 27 and 28, 29 and 30, 31 and 32, 33 and 34, 35 and 36, 37 and 38, 39 and 40, 41 and 42, 43 and 44, 45 and 46, 47 and 48, 49 and 50, 51 and 52, 53 and 54, 55 and 56, 57 and 58, 59 and 60, 61 and 62, 63 and 64, 65 and 66, 67 and 68, 69 and 70, 71 and 303, 304 and 74, 75 and 76, 77 and 78, 79 and 80, 81 and 82, 83 and 84, 85 and 86, 87 and 88, 89 and 90, and 91 and 92; wherein the CD8 α chain is SEQ ID NO: 7, 258, 259, 262, or a variant thereof; wherein, if present, the CD8 β chain is SEQ ID NO: 8, 9, 10, 11, 12, 13, or 14; and wherein the IL-15/IL-15R α fusion polypeptide is selected from (i) SEQ ID NO: 307 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 307, directly or indirectly fused to an N terminus of SEQ ID NO: 311 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 311, with or without a linker therebetween; (ii) SEQ ID NO: 307 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 307, directly or indirectly fused to an N terminus of SEQ ID NO: 313 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 313, with or without a linker therebetween; or (iii) SEQ ID NO: 307 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 307, directly or indirectly fused to an N terminus of SEQ ID NO: 315 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 315, with or without a linker therebetween may be provided.

[00145] In embodiments, the IL-15/IL-15R α fusion polypeptide may further comprise a signal peptide directly or indirectly fused to the N terminus of SEQ ID NO: 307 of any of (i), (ii), or (iii) or to the N terminus of a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 307 of any of (i), (ii), or (iii).

[00146] In embodiments, the signal peptide may be derived from an IgE polypeptide. In embodiments, the signal peptide derived from an IgE polypeptide may comprise SEQ ID NO: 367 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[00147] In embodiments, a T cell and/or natural killer cell comprising: (a) (i) a T-cell receptor (TCR) comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain and a

β chain, or (ii) a TCR comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain without a β chain, and (b) an IL-15/IL-15R α fusion polypeptide, wherein the TCR α chain and the TCR β chain are selected from SEQ ID NO: 15 and 16, 17 and 18, 19 and 20, 21 and 22, 23 and 24, 25 and 26, 27 and 28, 29 and 30, 31 and 32, 33 and 34, 35 and 36, 37 and 38, 39 and 40, 41 and 42, 43 and 44, 45 and 46, 47 and 48, 49 and 50, 51 and 52, 53 and 54, 55 and 56, 57 and 58, 59 and 60, 61 and 62, 63 and 64, 65 and 66, 67 and 68, 69 and 70, 71 and 303, 304 and 74, 75 and 76, 77 and 78, 79 and 80, 81 and 82, 83 and 84, 85 and 86, 87 and 88, 89 and 90, and 91 and 92; wherein the CD8 α chain is SEQ ID NO: 7, 258, 259, 262, or a variant thereof; wherein, if present, the CD8 β chain is SEQ ID NO: 8, 9, 10, 11, 12, 13, or 14; and wherein the IL-15/IL-15R α fusion polypeptide is selected from SEQ ID NO: 317, 319, 321, 323, 325, 327, 329, 331, 333, or 335, or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 317, 319, 321, 323, 325, 327, 329, 331, 333, or 335 may be provided.

[00148] In embodiments, the IL-15/IL-15R α fusion polypeptide may further comprise a signal peptide directly or indirectly fused to an N terminus of SEQ ID NO: 317, 319, 321, 323, 325, 327, 329, 331, 333, or 335, or directly or indirectly fused to an N terminus of a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 317, 319, 321, 323, 325, 327, 329, 331, 333, or 335.

[00149] In embodiments, a T cell and/or natural killer cell comprising: (a) (i) a T-cell receptor (TCR) comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain and a β chain, or (ii) a TCR comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain without a β chain, and (b) an IL-15/IL-15R α fusion polypeptide, wherein the TCR α chain and the TCR β chain are selected from SEQ ID NO: 15 and 16, 17 and 18, 19 and 20, 21 and 22, 23 and 24, 25 and 26, 27 and 28, 29 and 30, 31 and 32, 33 and 34, 35 and 36, 37 and 38, 39 and 40, 41 and 42, 43 and 44, 45 and 46, 47 and 48, 49 and 50, 51 and 52, 53 and 54, 55 and 56, 57 and 58, 59 and 60, 61 and 62, 63 and 64, 65 and 66, 67 and 68, 69 and 70, 71 and 303, 304 and 74, 75 and 76, 77 and 78, 79 and 80, 81 and 82, 83 and 84, 85 and 86, 87 and 88, 89 and 90, and 91 and 92; wherein the CD8 α chain is SEQ ID NO: 7, 258, 259, 262, or a variant thereof; wherein, if present, the CD8 β chain is SEQ ID NO: 8, 9, 10, 11, 12, 13, or 14; and wherein the IL-15/IL-15R α fusion polypeptide is selected from SEQ ID NO: 317, 319, 321, 323, 325, 327, 329, 331, or 333, or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 317, 319, 321, 323, 325, 327, 329, 331, or 333 may be provided.

[00150] In embodiments, the IL-15/IL-15R α fusion polypeptide may further comprise a signal peptide directly or indirectly fused to an N terminus of SEQ ID NO: 317, 319, 321, 323, 325, 327, 329, 331, or 333, or directly or indirectly fused to an N terminus of a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 317, 319, 321, 323, 325, 327, 329, 331, or 333.

[00151] In embodiments, the signal peptide may be derived from an IgE polypeptide. In embodiments, the signal peptide derived from an IgE polypeptide may comprise SEQ ID NO: 367 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[00152] In embodiments, a T cell and/or natural killer cell comprising: (a) (i) a T-cell receptor (TCR) comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain and a β chain, or (ii) a TCR comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain without a β chain, and (b) a fusion polypeptide comprising (i) a signal peptide comprising SEQ ID NO: 367 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 367 fused to (ii) an IL-15/IL-15R α fusion polypeptide, wherein the TCR α chain and the TCR β chain are selected from SEQ ID NO: 15 and 16, 17 and 18, 19 and 20, 21 and 22, 23 and 24, 25 and 26, 27 and 28, 29 and 30, 31 and 32, 33 and 34, 35 and 36, 37 and 38, 39 and 40, 41 and 42, 43 and 44, 45 and 46, 47 and 48, 49 and 50, 51 and 52, 53 and 54, 55 and 56, 57 and 58, 59 and 60, 61 and 62, 63 and 64, 65 and 66, 67 and 68, 69 and 70, 71 and 303, 304 and 74, 75 and 76, 77 and 78, 79 and 80, 81 and 82, 83 and 84, 85 and 86, 87 and 88, 89 and 90, and 91 and 92; wherein the CD8 α chain is SEQ ID NO: 7, 258, 259, 262, or a variant thereof; wherein, if present, the CD8 β chain is SEQ ID NO: 8, 9, 10, 11, 12, 13, or 14; and wherein the fusion polypeptide of (b) is selected from SEQ ID NO: 337, 339, 341, 343, 345, 347, 349, 351, 353, or 355, or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 337, 339, 341, 343, 345, 347, 349, 351, 353, or 355 may be provided.

[00153] In embodiments, a T cell and/or natural killer cell comprising: (a) (i) a T-cell receptor (TCR) comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain and a β chain, or (ii) a TCR comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain without a β chain, and (b) a fusion polypeptide comprising (i) a signal peptide comprising SEQ ID NO: 367 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 367 fused to (ii) an IL-15/IL-15R α fusion polypeptide, wherein the TCR α chain and the TCR β chain are selected from SEQ ID NO: 15 and 16, 17 and 18, 19 and 20, 21 and 22, 23 and 24, 25 and 26, 27

and 28, 29 and 30, 31 and 32, 33 and 34, 35 and 36, 37 and 38, 39 and 40, 41 and 42, 43 and 44, 45 and 46, 47 and 48, 49 and 50, 51 and 52, 53 and 54, 55 and 56, 57 and 58, 59 and 60, 61 and 62, 63 and 64, 65 and 66, 67 and 68, 69 and 70, 71 and 303, 304 and 74, 75 and 76, 77 and 78, 79 and 80, 81 and 82, 83 and 84, 85 and 86, 87 and 88, 89 and 90, and 91 and 92; wherein the CD8 α chain is SEQ ID NO: 7, 258, 259, 262, or a variant thereof; wherein, if present, the CD8 β chain is SEQ ID NO: 8, 9, 10, 11, 12, 13, or 14; and wherein the fusion polypeptide of (b) is selected from SEQ ID NO: 337, 339, 341, 343, 345, 347, 349, 351, or 353, or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 337, 339, 341, 343, 345, 347, 349, 351, or 353 may be provided.

[00154] In embodiments, a T cell and/or natural killer cell transduced to express (a) (i) a T-cell receptor (TCR) comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain and a β chain, or (ii) a TCR comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain without a β chain, and (b) an IL-15/IL-15R α fusion polypeptide, wherein the TCR α chain and the TCR β chain are selected from SEQ ID NO: 15 and 16, 17 and 18, 19 and 20, 21 and 22, 23 and 24, 25 and 26, 27 and 28, 29 and 30, 31 and 32, 33 and 34, 35 and 36, 37 and 38, 39 and 40, 41 and 42, 43 and 44, 45 and 46, 47 and 48, 49 and 50, 51 and 52, 53 and 54, 55 and 56, 57 and 58, 59 and 60, 61 and 62, 63 and 64, 65 and 66, 67 and 68, 69 and 70, 71 and 303, 304 and 74, 75 and 76, 77 and 78, 79 and 80, 81 and 82, 83 and 84, 85 and 86, 87 and 88, 89 and 90, and 91 and 92; wherein the CD8 α chain is SEQ ID NO: 7, 258, 259, 262, or a variant thereof; wherein, if present, the CD8 β chain is SEQ ID NO: 8, 9, 10, 11, 12, 13, or 14; and wherein the IL-15/IL-15R α fusion polypeptide is selected from SEQ ID NO: 317, 321, 325, 327, 329, 331, 333, or 335 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 317, 321, 325, 327, 329, 331, 333, or 335 may be provided.

[00155] In embodiments, the IL-15/IL-15R α fusion polypeptide may further comprise a signal peptide directly or indirectly fused to an N terminus of SEQ ID NO: SEQ ID NO: 317, 321, 325, 327, 329, 331, 333, or 335, or directly or indirectly fused to an N terminus of a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 317, 321, 325, 327, 329, 331, 333, or 335.

[00156] In embodiments, a T cell and/or natural killer cell transduced to express (a) (i) a T-cell receptor (TCR) comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain and a β chain, or (ii) a TCR comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain without a β chain, and (b) an IL-15/IL-15R α fusion polypeptide, wherein the TCR α chain and the TCR β chain are selected from SEQ ID NO: 15 and 16, 17 and 18, 19

and 20, 21 and 22, 23 and 24, 25 and 26, 27 and 28, 29 and 30, 31 and 32, 33 and 34, 35 and 36, 37 and 38, 39 and 40, 41 and 42, 43 and 44, 45 and 46, 47 and 48, 49 and 50, 51 and 52, 53 and 54, 55 and 56, 57 and 58, 59 and 60, 61 and 62, 63 and 64, 65 and 66, 67 and 68, 69 and 70, 71 and 303, 304 and 74, 75 and 76, 77 and 78, 79 and 80, 81 and 82, 83 and 84, 85 and 86, 87 and 88, 89 and 90, and 91 and 92; wherein the CD8 α chain is SEQ ID NO: 7, 258, 259, 262, or a variant thereof; wherein, if present, the CD8 β chain is SEQ ID NO: 8, 9, 10, 11, 12, 13, or 14; and wherein the IL-15/IL-15R α fusion polypeptide is selected from SEQ ID NO: 317, 321, 325, 327, 329, 331, or 333 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 317, 321, 325, 327, 329, 331, or 333 may be provided.

[00157] In embodiments, the IL-15/IL-15R α fusion polypeptide may further comprise a signal peptide directly or indirectly fused to an N terminus of SEQ ID NO: 317, 321, 325, 327, 329, 331, or 333, or directly or indirectly fused to an N terminus of a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 317, 321, 325, 327, 329, 331, or 333.

[00158] In embodiments, the signal peptide may be derived from an IgE polypeptide. In embodiments, the signal peptide derived from an IgE polypeptide may comprise SEQ ID NO: 367 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[00159] In embodiments, a T cell and/or natural killer cell comprising: (a) (i) a T-cell receptor (TCR) comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain and a β chain, or (ii) a TCR comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain without a β chain, and (b) a fusion polypeptide comprising (i) a signal peptide comprising SEQ ID NO: 367 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 367 directly or indirectly fused to (ii) an IL-15/IL-15R α fusion polypeptide, wherein the TCR α chain and the TCR β chain are selected from SEQ ID NO: 15 and 16, 17 and 18, 19 and 20, 21 and 22, 23 and 24, 25 and 26, 27 and 28, 29 and 30, 31 and 32, 33 and 34, 35 and 36, 37 and 38, 39 and 40, 41 and 42, 43 and 44, 45 and 46, 47 and 48, 49 and 50, 51 and 52, 53 and 54, 55 and 56, 57 and 58, 59 and 60, 61 and 62, 63 and 64, 65 and 66, 67 and 68, 69 and 70, 71 and 303, 304 and 74, 75 and 76, 77 and 78, 79 and 80, 81 and 82, 83 and 84, 85 and 86, 87 and 88, 89 and 90, and 91 and 92; wherein the CD8 α chain is SEQ ID NO: 7, 258, 259, 262, or a variant thereof; wherein, if present, the CD8 β chain is SEQ ID NO: 8, 9, 10, 11, 12, 13, or 14; and wherein the fusion polypeptide of (b) is selected from SEQ ID NO: 337, 341, 345, 347, 349, 351, or 353, or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least

about 99%, or about 100% identical to SEQ ID NO: 337, 341, 345, 347, 349, 351, or 353 may be provided.

[00160] In embodiments, a T cell and/or natural killer cell comprising: (a) (i) a T-cell receptor (TCR) comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain and a β chain, or (ii) a TCR comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain without a β chain, and (b) an IL-15/IL-15R α fusion polypeptide, wherein the TCR α chain and the TCR β chain are selected from SEQ ID NO: 15 and 16, 57 and 58, 59 and 60, 61 and 62, 63 and 64, 65 and 66, 67 and 68, 69 and 70, and 71 and 303; wherein the CD8 α chain is SEQ ID NO: 7, 258, 259, 262, or a variant thereof; and wherein, if present, the CD8 β chain is SEQ ID NO: 8, 9, 10, 11, 12, 13, or 14.

[00161] In embodiments, the IL-15/IL-15R α fusion polypeptide may comprise SEQ ID NO: 317 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[00162] In embodiments, the IL-15/IL-15R α fusion polypeptide may comprise SEQ ID NO: 319 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[00163] In embodiments, the IL-15/IL-15R α fusion polypeptide may comprise SEQ ID NO: 321 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[00164] In embodiments, the IL-15/IL-15R α fusion polypeptide may comprise SEQ ID NO: 323 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[00165] In embodiments, the IL-15/IL-15R α fusion polypeptide may comprise SEQ ID NO: 325 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[00166] In embodiments, the IL-15/IL-15R α fusion polypeptide may comprise SEQ ID NO: 327 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[00167] In embodiments, the IL-15/IL-15R α fusion polypeptide may comprise SEQ ID NO: 329 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[00168] In embodiments, the IL-15/IL-15R α fusion polypeptide may comprise SEQ ID NO: 331 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[00169] In embodiments, the IL-15/IL-15R α fusion polypeptide may comprise SEQ ID NO: 333 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[00170] In embodiments, the IL-15/IL-15R α fusion polypeptide may comprise SEQ ID NO: 335 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[00171] In embodiments, the IL-15/IL-15R α fusion polypeptide may further comprise a signal peptide directly or indirectly fused to an N terminus of the IL-15/IL-15R α fusion polypeptide. In embodiments, the signal peptide may be derived from an IgE polypeptide. In embodiments, the signal peptide derived from an IgE polypeptide may comprise SEQ ID NO: 367 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[00172] In embodiments, T cell and/or natural killer cell comprising: (a) (i) a T-cell receptor (TCR) comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain and a β chain, or (ii) a TCR comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain without a β chain, and (b) a fusion polypeptide comprising (i) SEQ ID NO: 367 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 367 fused to (ii) an N terminus of an IL-15/IL-15R α fusion polypeptide, wherein the TCR α chain and the TCR β chain are selected from SEQ ID NO: 15 and 16, 57 and 58, 59 and 60, 61 and 62, 63 and 64, 65 and 66, 67 and 68, 69 and 70, and 71 and 303; wherein the CD8 α chain is SEQ ID NO: 7, 258, 259, 262, or a variant thereof; and wherein, if present, the CD8 β chain is SEQ ID NO: 8, 9, 10, 11, 12, 13, or 14.

[00173] In embodiments, the fusion polypeptide of (b) may comprise SEQ ID NO: 337 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[00174] In embodiments, the fusion polypeptide of (b) may comprise SEQ ID NO: 339 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[00175] In embodiments, the fusion polypeptide of (b) may comprise SEQ ID NO: 341 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[00176] In embodiments, the fusion polypeptide of (b) may comprise SEQ ID NO: 343 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[00177] In embodiments, the fusion polypeptide of (b) may comprise SEQ ID NO: 345 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[00178] In embodiments, the fusion polypeptide of (b) may comprise SEQ ID NO: 347 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[00179] In embodiments, the fusion polypeptide of (b) may comprise SEQ ID NO: 349 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[00180] In embodiments, the fusion polypeptide of (b) may comprise SEQ ID NO: 351 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[00181] In embodiments, the fusion polypeptide of (b) may comprise SEQ ID NO: 353 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[00182] In embodiments, the fusion polypeptide of (b) may comprise SEQ ID NO: 355 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[00183] In embodiments, the T cell may be an $\alpha\beta$ T cell, a $\gamma\delta$ T cell, a natural killer T cell, or any combination thereof. In embodiments, the $\alpha\beta$ T cell may be a CD4⁺ T cell. In embodiments, the $\alpha\beta$ T cell may be a CD8⁺ T cell. In embodiments, the $\gamma\delta$ T cell may be a V γ 9V δ 2⁺ T cell.

[00184] In embodiments, a composition comprising a T cell and/or natural killer cell described herein may be provided. In embodiments, the composition may be a pharmaceutical composition. In embodiments, the composition may further comprise an adjuvant, excipient, carrier, diluent, buffer, stabilizer, or a combination thereof.

[00185] In embodiments, the adjuvant may be an anti-CD40 antibody, imiquimod, resiquimod, GM-CSF, cyclophosphamide, sunitinib, bevacizumab, atezolizumab, interferon-alpha, interferon-beta, CpG oligonucleotides and derivatives, poly(I:C) and derivatives, RNA, sildenafil, particulate formulations with poly(lactide co-glycolide) (PLG), virosomes, interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-4 (IL-4), interleukin-7 (IL-7), interleukin-12 (IL-12), interleukin-13 (IL-13), interleukin-15 (IL-15), interleukin-21 (IL-21), interleukin-23 (IL-23), or any combination thereof. In embodiments, the adjuvant may be IL-2, IL-7, IL-12, IL-15, IL-21, or any combination thereof.

[00186] In embodiments, a method of preparing T cells and/or natural killer cells for immunotherapy may be provided, the method comprising: isolating T cells and/or natural killer

cells from a blood sample of a human subject, activating the isolated T cells and/or natural killer cells, transducing the activated T cells and/or natural killer cells with a nucleic acid described herein or a vector described herein, and expanding the transduced T cells and/or natural killer cells. In embodiments, the method may further comprise isolating CD4⁺CD8⁺ T cells from the transduced T cells and/or natural killer cells and expanding the isolated CD4⁺CD8⁺ transduced T cells. In embodiments, the blood sample may comprise peripheral blood mononuclear cells (PMBC). In embodiments, the activating may comprise contacting the T cells and/or natural killer cells with an anti-CD3 and an anti-CD28 antibody. In embodiments, the T cell may be a CD4⁺ T cell. In embodiments, the T cell may be a CD8⁺ T cell. In embodiments, the T cell may be a $\gamma\delta$ T cell or an $\alpha\beta$ T cell. In embodiments, the activation, the expanding, or both may be in the presence of a combination of IL-2 and IL-15 and optionally with zoledronate.

[00187] In embodiments, a method of increasing persistence, functionality, naivety, longevity, capacity to kill antigen-presenting cells, or a combination thereof, of T cells and/or natural killer cells may be provided, the method comprising: isolating T cells and/or natural killer cells from a blood sample of a human subject, activating the isolated T cells and/or natural killer cells, transducing the activated T cells and/or natural killer cells with a nucleic acid described herein, a vector described herein, or a combination thereof, to obtain transduced T cells and/or natural killer cells, and obtaining the transduced T cells and/or natural killer cells, wherein the persistence, longevity, naivety, capacity to kill antigen-presenting cells, or a combination thereof of the transduced T cells and/or natural killer cells is increased as compared with that of control cells. In embodiments, the method may further comprise expanding the transduced T cells and/or natural killer cells.

[00188] In embodiments, the control cells may comprise non-transduced T cells and/or natural killer cells, T cells and/or natural killer cells transduced with TCR only, or a combination thereof. In embodiments, the control may cells comprise non-transduced T cells and/or natural killer cells, T cells and/or natural killer cells transduced with TCR only, T cells and/or natural killer cells transduced with TCR and CD8 only, or a combination thereof. In embodiments, the persistence, longevity, functionality, naivety, capacity to kill antigen-presenting cells, or a combination thereof of the transduced T cells and/or natural killer cells and control cells may be determined after one challenge with antigen-presenting cells, two challenges with antigen-presenting cells, three challenges with antigen-presenting cells, four challenges with antigen-presenting cells, five challenges with antigen-presenting cells, six challenges with antigen-presenting cells, seven challenges with antigen-presenting cells, or more challenges with antigen-presenting cells. the persistence, longevity, functionality, naivety, capacity to kill antigen-presenting cells, or a combination thereof of the transduced T cells and/or natural killer cells and

control cells may be determined after five or more challenges with antigen-presenting cells or more challenges with antigen-presenting cells.

[00189] In embodiments, a method of increasing interferon γ (IFN γ) secretion by T cells and/or natural killer cells may be provided, the method comprising: isolating T cells and/or natural killer cells from a blood sample of a human subject, activating the isolated T cells and/or natural killer cells, transducing the activated T cells and/or natural killer cells with a nucleic acid described herein, a vector described herein, or a combination thereof, to obtain transduced T cells and/or natural killer cells, and obtaining the transduced T cells and/or natural killer cells, wherein the IFN γ secretion of the transduced T cells and/or natural killer cells is increased as compared with that of control cells. In embodiments, the method may further comprise expanding the transduced T cells and/or natural killer cells. In embodiments, the control cells may comprise non-transduced T cells and/or natural killer cells, T cells and/or natural killer cells transduced with TCR only, or a combination thereof.

[00190] In embodiments, the control cells may comprise non-transduced T cells and/or natural killer cells, T cells and/or natural killer cells transduced with TCR only, T cells and/or natural killer cells transduced with TCR and CD8 only, or a combination thereof. In embodiments, the IFN γ secretion by the transduced T cells and/or natural killer cells and control cells may be determined after one challenge with antigen-presenting cells, two challenges with antigen-presenting cells, three challenges with antigen-presenting cells, four challenges with antigen-presenting cells, five challenges with antigen-presenting cells, six challenges with antigen-presenting cells, seven challenges with antigen-presenting cells, or more challenges with antigen-presenting cells. In embodiments, the IFN γ secretion by the transduced T cells and/or natural killer cells and control cells may be determined after five or more challenges with antigen-presenting cells or more challenges with antigen-presenting cells.

[00191] In embodiments, the antigen presenting cells may present an antigen on a cell surface, and the transduced T cells and/or natural killer cells and control cells may be capable of killing the antigen presenting cells. In embodiments, the antigen may comprise a peptide. In embodiments, the peptide may be in a complex with an MHC molecule on the cell surface.

[00192] In embodiments, a polypeptide, polypeptides, or fusion polypeptide encoded by a nucleic acid described herein may be provided.

[00193] In embodiments, a nucleic acid described herein may be isolated, recombinant, or both isolated and recombinant.

[00194] In embodiments, a vector described herein may be isolated, recombinant, or both isolated and recombinant.

[00195] In embodiments, a T cell and/or natural killer cell described herein may be isolated, recombinant, engineered, or any combination thereof.

[00196] In embodiments, a polypeptide, polypeptides, or fusion polypeptide described herein may be isolated, recombinant, or both isolated and recombinant.

[00197] In embodiments, a vector comprising a nucleic acid described herein may be provided. In embodiments, a vector described herein may further comprise a nucleic acid encoding a 2A peptide or an internal ribosome entry site (IRES) positioned between a nucleic acid encoding a CD8 α chain and a nucleic acid encoding a CD8 β chain. In embodiments, the vector may further comprise a nucleic acid encoding a 2A peptide or an IRES positioned between a nucleic acid encoding a TCR α chain and a nucleic acid encoding a TCR β chain. In embodiments, the vector may further comprise a nucleic acid encoding a 2A peptide or an IRES positioned between a nucleic acid encoding a TCR chain or a CD8 chain and a nucleic acid encoding a membrane-bound IL-15, such as an IL-15/IL-15R α fusion polypeptide. In embodiments, the 2A peptide may be P2A (SEQ ID NO: 93), T2A (SEQ ID NO: 94), E2A (SEQ ID NO: 95), or F2A (SEQ ID NO: 96). In embodiments, the IRES may be selected from the group consisting of IRES from picornavirus, IRES from flavivirus, IRES from pestivirus, IRES from retrovirus, IRES from lentivirus, IRES from insect RNA virus, and IRES from cellular mRNA. In embodiments, the vector may further comprise a post-transcriptional regulatory element (PRE) sequence selected from a Woodchuck PRE (WPRES) (SEQ ID NO: 264), Woodchuck PRE (WPRES) mutant 1 (SEQ ID NO: 256), Woodchuck PRE (WPRES) mutant 2 (SEQ ID NO: 257), or hepatitis B virus (HBV) PRE (HPRES) (SEQ ID NO: 437). In embodiments, the post-transcriptional regulatory element (PRE) sequence may be a Woodchuck PRE (WPRES) mutant 1 comprising the nucleic acid sequence of SEQ ID NO: 256. In embodiments, the post-transcriptional regulatory element (PRE) sequence may be a Woodchuck PRE (WPRES) mutant 2 comprising the nucleic acid sequence of SEQ ID NO: 257. In embodiments, the vector may further comprise a promoter selected from cytomegalovirus (CMV) promoter, phosphoglycerate kinase (PGK) promoter, myelin basic protein (MBP) promoter, glial fibrillary acidic protein (GFAP) promoter, modified MoMuLV LTR comprising myeloproliferative sarcoma virus enhancer (MNDU3), Ubiquitin C promoter, EF-1 alpha promoter, or Murine Stem Cell Virus (MSCV) promoter. In embodiments, the promoter may be a Murine Stem Cell Virus (MSCV) promoter. In embodiments, vector may be a viral vector or a non-viral vector. In embodiments, the vector may be a viral vector. In embodiments, the viral vector may be selected from adenoviruses, poxviruses, alphaviruses, arenaviruses, flaviviruses, rhabdoviruses, retroviruses, lentiviruses, herpesviruses, paramyxoviruses, picornaviruses, and any combination thereof. In embodiments, the viral vector may be pseudotyped with an envelope

protein of a virus selected from the native feline endogenous virus (RD114), a version of RD114 (RD114TR), gibbon ape leukemia virus (GALV), a version of GALV (GALV-TR), amphotropic murine leukemia virus (MLV 4070A), baculovirus (GP64), vesicular stomatitis virus (VSV-G), fowl plague virus (FPV), Ebola virus (EboV), or baboon retroviral envelope glycoprotein (BaEV), and lymphocytic choriomeningitis virus (LCMV). In embodiments, the vector may be a lentiviral vector. In embodiments, the vector may further comprise a nucleic acid encoding a chimeric antigen receptor (CAR).

[00198] In embodiments, a T cell and/or natural killer cell expressing a polypeptide as described herein and/or comprising a vector described herein and/or produced by a method described herein may be provided. In embodiments, the T cell may be an $\alpha\beta$ T cell, a $\gamma\delta$ T cell, a natural killer T cell, or any combination thereof. In embodiments, the $\alpha\beta$ T cell may be a CD4⁺ T cell. In embodiments, the $\alpha\beta$ T cell may be a CD8⁺ T cell. In embodiments, the $\gamma\delta$ T cell may be a V γ 9V δ 2⁺ T cell.

[00199] In embodiments, a composition comprising a T cell and/or natural killer cell described herein may be provided. In embodiments, the composition may be a pharmaceutical composition. In embodiments, the composition may further comprise an adjuvant, excipient, carrier, diluent, buffer, stabilizer, or a combination thereof. In embodiments, the adjuvant may be an anti-CD40 antibody, imiquimod, resiquimod, GM-CSF, cyclophosphamide, sunitinib, bevacizumab, atezolizumab, interferon-alpha, interferon-beta, CpG oligonucleotides and derivatives, poly(I:C) and derivatives, RNA, sildenafil, particulate formulations with poly(lactide co-glycolide) (PLG), virosomes, interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-4 (IL-4), interleukin-7 (IL-7), interleukin-12 (IL-12), interleukin-13 (IL-13), interleukin-15 (IL-15), interleukin-21 (IL-21), interleukin-23 (IL-23), or any combination thereof. In embodiments, the adjuvant may be IL-2, IL-7, IL-12, IL-15, IL-21, or any combination thereof.

[00200] In embodiments, a method of treating a patient who has cancer may be provided, the method comprising administering to the patient a composition described herein, wherein the cancer is selected from the group consisting of non-small cell lung cancer, small cell lung cancer, melanoma, liver cancer, breast cancer, uterine cancer, Merkel cell carcinoma, pancreatic cancer, gallbladder cancer, bile duct cancer, colorectal cancer, urinary bladder cancer, kidney cancer, leukemia, ovarian cancer, esophageal cancer, brain cancer, gastric cancer, and prostate cancer. In embodiments, a method of eliciting an immune response in a patient who has cancer may be provided, the method comprising administering to the patient a composition described herein, wherein the cancer is selected from the group consisting of non-small cell lung cancer, small cell lung cancer, melanoma, liver cancer, breast cancer, uterine cancer, Merkel cell carcinoma, pancreatic cancer, gallbladder cancer, bile duct cancer, colorectal cancer, urinary bladder cancer,

kidney cancer, leukemia, ovarian cancer, esophageal cancer, brain cancer, gastric cancer, and prostate cancer. In embodiments, the T cell and/or natural killer cell may kill cancer cells that present a peptide in a complex with an MHC molecule on a cell surface.

[00201] In embodiments, nucleic acid sequences disclosed herein may be mutated such that the amino acids encoded remain the same, but the nucleic acid codons are changed to maintain improved expression in a target cell and/or by a target vector. In embodiments, nucleic acids disclosed herein may be codon optimized. In embodiments, nucleic acid sequences set forth herein are codon optimized. In embodiments, nucleic acid sequences set forth herein may be codon optimized, and nucleic acid sequences encoding polypeptides set forth herein may be codon optimized. In embodiments, mutation of nucleic acid sequences set forth herein may encompass codon optimization.

[00202] In embodiments, expression of membrane-bound IL-15 may improve immune cell, such as but not limited to, T cell and/or natural killer cell, persistence, functionality, growth, viability, expansion, or any combination thereof, as compared to cells not expressing membrane-bound IL-15. In embodiments, expression of membrane-bound IL-15 may improve immune cell, such as but not limited to, T cell and/or natural killer cell, persistence, functionality, growth, viability, expansion, or any combination thereof, in a tumor microenvironment, as compared to cells not expressing membrane-bound IL-15. In embodiments, expression of membrane-bound IL-15 may increase efficacy of immune cells, such as, but not limited to, T cells and/or natural killer cells, in killing tumor cells, as compared to cells not expressing membrane-bound IL-15. In embodiments, expression of membrane-bound IL-15 may increase ability of immune cells, such as, but not limited to, T cells and/or natural killer cells, to survive in a tumor microenvironment, to persist in killing tumor cells, or any combination thereof, as compared to cells not expressing membrane-bound IL-15. In embodiments, expression of membrane-bound IL-15 may increase ability of immune cells, such as, but not limited to, T cells and/or natural killer cells, to maintain a naive phenotype.

[00203] Persistence may be assessed, as a non-limiting example, by the length of time cells are detectable in an individual (e.g., patient) after infusion. As non-limiting examples, persistence may be measured at days, weeks, months, or years after infusion, as non-limiting examples, at about 1 week, about 2 weeks, about 4 weeks, about 1 month, about 2 months, about 3 months, about 6 months, about 9 months, about 12 months, about 18 months, about 24 months, and/or about 30 months after infusion. Persistence may be assessed, as non-limiting examples, by PCR of peripheral blood sample(s), by flow cytometry of peripheral blood samples(s), and/or by analysis of tumor biopsy sample(s). Persistence of cells expressing membrane-bound IL-15

may be compared, as non-limiting examples, to typical persistence of infused ACT cells or persistence of similar cells not expressing membrane-bound IL-15.

[00204] Continued ability to kill tumor cells may be measured, as non-limiting examples, via (i) serial killing assays using an IncuCyte (wherein ability to kill/impair tumor growth as measured by fold growth during repeated tumor stimulations over a duration of time is assessed), and/or (ii) via cytokine/effector molecule production (IFN γ via ELISAs and other pro-inflammatory cytokines via Luminex (cytokines measured may include, as non-limiting examples, IFN γ , TNF α , Granzyme B, perforin, IL-2, IL-6, MIP-1 β , MIP-1 α , GM-CSF, RANTES, IL-18, IL-4, IL-10, and IP10)). Continued ability of cells expressing membrane-bound IL-15 to kill tumor cells may be compared, as non-limiting examples, to continued ability of similar cells not expressing membrane-bound IL-15 to kill tumor cells or continued ability of other control cells to kill tumor cells.

[00205] Naivety of phenotype may be assessed, as a non-limiting example, via Tmem panel assay via flow cytometry. Typically, flow cytometer gating is off of CD8+TCR+ cells. Typically, a more naïve phenotype may be indicated by higher frequencies of the T memory subsets Tnaïve/scm (CD45RA+CCR7+), and Tcm (CD45RA-CCR7+) and an increase or retention of the CD39-CD69- and CD27+CD28+ populations. Low CD57 expression may also be desirable.

[00206] When assessing the persistence, functionality, growth, viability, expansion, tumor killing efficacy, naivety, or other characteristics of cells expressing dnTGFR β RIL, cells such as non-transduced cells, cells transduced with TCR only, cells transduced with CD8 and TCR, or a combination thereof, may serve as control cells, as non-limiting examples.

[00207] In embodiments, membrane-bound IL-15 may act in a *cis* manner (e.g., affecting cells in which it is expressed), in a *trans* manner (e.g., affecting cells in which it is not expressed), or any combination thereof. In embodiments in which membrane-bound IL-15 acts in *trans*, cells adjacent to or near (e.g., within the tumor microenvironment) cells expressing membrane-bound IL-15 may exhibit any or combination of improvements the same or similar to those described for cells expressing membrane-bound IL-15, as compared to cells not adjacent to or near cells expressing membrane-bound IL-15.

[00208] In embodiments, the disclosure provides for nucleic acid(s) encoding polypeptide(s) described herein. In embodiments, the disclosure provides for vectors comprising nucleic acids encoding polypeptide(s) described herein. In embodiments, one or more vector may comprise a nucleic acid encoding an IL-15/IL-15R α fusion polypeptide. In embodiments, one or more vector may comprise a nucleic acid encoding a CD8 polypeptide. In embodiments, one or more vector

may comprise a nucleic acid encoding a CD8 α polypeptide. In embodiments, one or more vector may comprise a nucleic acid encoding a CD8 β polypeptide.

[00209] In embodiments, one or more vector may comprise one or more nucleic acid encoding a T cell receptor (TCR) comprising an α chain and a β chain. In embodiments, one or more vector may comprise one or more nucleic acid encoding a T cell receptor (TCR) comprising an γ chain and a δ chain. In embodiments, one or more vector may comprise one or more nucleic acid encoding a chimeric antigen receptor (CAR).

[00210] In embodiments, a vector or vectors comprising one or more nucleic acid(s) encoding one or any combination of a TCR comprising an α chain and a β chain, a TCR comprising a γ chain and a δ chain, a CAR, an IL-15 polypeptide, an IL-15R α polypeptide, an IL-15/IL-15R α fusion polypeptide, and/or a CD8 polypeptide may be provided. In embodiments, a CD8 polypeptide may comprise a CD8 α chain and/or a CD8 β chain, and the CD8 α chain and/or CD8 β chain may independently be modified or unmodified.

[00211] In embodiments, a vector or vectors comprising one or more nucleic acid(s) encoding one or any combination of a TCR comprising an α chain and a β chain, an IL-15/IL-15R α fusion polypeptide, and/or a CD8 polypeptide may be provided. In embodiments, a vector or vectors comprising one or more nucleic acid(s) encoding one or any combination of a TCR comprising a γ chain and a δ chain, an IL-15/IL-15R α fusion polypeptide, and/or a CD8 polypeptide may be provided. In embodiments, a vector or vectors comprising one or more nucleic acid(s) encoding one or any combination of a CAR, an IL-15/IL-15R α fusion polypeptide, and/or a CD8 polypeptide may be provided. In embodiments, a CD8 polypeptide may comprise a CD8 α chain and/or a CD8 β chain, and the CD8 α chain and/or CD8 β chain may independently be modified or unmodified.

[00212] In embodiments, a vector or vectors comprising one or more nucleic acid(s) encoding a TCR comprising an α chain and a β chain, an IL-15/IL-15R α fusion polypeptide, and a CD8 polypeptide may be provided. In embodiments, a vector or vectors comprising one or more nucleic acid(s) encoding a TCR comprising a γ chain and a δ chain, an IL-15/IL-15R α fusion polypeptide, and a CD8 polypeptide may be provided. In embodiments, a vector or vectors comprising one or more nucleic acid(s) encoding a CAR, an IL-15/IL-15R α fusion polypeptide, and a CD8 polypeptide may be provided. In embodiments, a CD8 polypeptide may comprise a CD8 α chain and/or a CD8 β chain, and the CD8 α chain and/or CD8 β chain may independently be modified or unmodified.

[00213] In embodiments, a vector or vectors comprising one or more nucleic acid(s) encoding a TCR comprising an α chain and a β chain and an IL-15/IL-15R α fusion polypeptide may be

provided. In embodiments, a vector or vectors comprising one or more nucleic acid(s) encoding a TCR comprising a γ chain and a δ chain and an IL-15/IL-15R α fusion polypeptide may be provided. In embodiments, a vector or vectors comprising one or more nucleic acid(s) encoding a CAR and an IL-15/IL-15R α fusion polypeptide may be provided.

[00214] In embodiments, a vector or vectors comprising one or more nucleic acid(s) encoding a TCR comprising an α chain and a β chain and a CD8 polypeptide may be provided. In embodiments, a vector or vectors comprising one or more nucleic acid(s) encoding a TCR comprising a γ chain and a δ chain and a CD8 polypeptide may be provided. In embodiments, a cell or cells comprising one or more nucleic acid(s) encoding a CAR and a CD8 polypeptide may be provided. In embodiments, a CD8 polypeptide may comprise a CD8 α chain and/or a CD8 β chain, and the CD8 α chain and/or CD8 β chain may independently be modified or unmodified.

[00215] In embodiments, more than one vector may be co-transduced into one or more cells, co-expressed in one or more cells, or any combination thereof. In embodiments, a cell or cells may comprise an $\alpha\beta$ T cell, a $\gamma\delta$ T cell, a natural killer (NK) cell, a natural killer T cell, a CD4+ T cell, CD8+ T cell, a CD4+ /CD8+ cell, or any combination thereof.

[00216] In embodiments, more than one vector may comprise a nucleic acid or nucleic acids encoding one or any combination of an IL-15 polypeptide, an IL-15R α polypeptide, an IL-15/IL-15R α fusion polypeptide, a CD8 polypeptide, a TCR comprising an α chain and a β chain, a TCR comprising a γ chain and a δ chain, and/or a CAR. In embodiments, a CD8 polypeptide may comprise a CD8 α chain and/or a CD8 β chain, and the CD8 α chain and/or CD8 β chain may independently be modified or unmodified.

[00217] In embodiments, a single vector may comprise a nucleic acid or nucleic acids encoding one or any combination of an IL-15 polypeptide, an IL-15R α polypeptide, an IL-15/IL-15R α fusion polypeptide, a CD8 polypeptide, a TCR comprising an α chain and a β chain, a TCR comprising a γ chain and a δ chain, and/or a CAR. In embodiments, a CD8 polypeptide may comprise a CD8 α chain and/or a CD8 β chain, and the CD8 α chain and/or CD8 β chain may independently be modified or unmodified.

[00218] In embodiments, nucleic acids may be polycistronic, and one or more polycistronic nucleic acids may be utilized. Expression of multiple (e.g., 2, 3, 4, 5, or more) polypeptides from polycistronic nucleic acid may be achieved by any suitable method, such as i) pre-mRNA splicing; ii) proteolytic cleavage sites; iii) fusion proteins; iv) inclusion of one or more 2A peptide-encoding nucleic acid(s) (such as, but not limited to P2A, T2A, E2A, and F2A), v) inclusion of one or more internal ribosome entry site (IRES), ~~or other mechanisms, as well~~. Each of these approaches has some advantages and disadvantages to provide multiple transcription

units. Among the five approaches, the most widely used are the self-cleaving 2A peptides and IRESs. In embodiments, nucleic acids may be monocistronic, and one or more monocistronic nucleic acid(s) may be utilized.

[00219] In embodiments, a 2A peptide may be selected from P2A (SEQ ID NO: 93), T2A (SEQ ID NO: 94), E2A (SEQ ID NO: 95), or F2A (SEQ ID NO: 96).

[00220] In embodiments, an IRES may be selected from the group consisting of IRES from picornavirus, IRES from flavivirus, IRES from pestivirus, IRES from retrovirus, IRES from lentivirus, IRES from insect RNA virus, and IRES from cellular mRNA.

[00221] In embodiments, a vector may comprise nucleic acid encoding a 2A peptide or an internal ribosome entry site (IRES) positioned between a nucleic acid encoding a modified CD8 α polypeptide and a nucleic acid encoding a CD8 β polypeptide.

[00222] In embodiments, a vector may comprise nucleic acid encoding a 2A peptide positioned between a nucleic acid encoding a TCR α chain and a nucleic acid encoding a TCR β chain.

[00223] In embodiments, a vector may comprise nucleic acid encoding a 2A peptide or an internal ribosome entry site (IRES) positioned between a nucleic acid encoding a modified CD8 α polypeptide, a nucleic acid encoding a CD8 β polypeptide, a nucleic acid encoding a TCR α chain, or a nucleic acid encoding a TCR β chain and a nucleic acid encoding a membrane-bound IL-15.

[00224] In embodiments, a single vector may comprise a nucleic acid or nucleic acids encoding one or any combination of an IL-15 polypeptide, an IL-15R α polypeptide, an IL-15/IL-15R α fusion polypeptide, a CD8 polypeptide, a TCR comprising an α chain and a β chain, a TCR comprising an γ chain and a δ chain, and/or a CAR, and a vector may comprise a nucleic acid encoding a 2A peptide or an internal ribosome entry site (IRES) positioned between any or each of nucleic acids encoding polypeptides or fusion polypeptides. In embodiments, a CD8 polypeptide may comprise a CD8 α chain and/or a CD8 β chain, and the CD8 α chain and/or CD8 β chain may independently be modified or unmodified.

[00225] In embodiments, a vector may further comprise a post-transcriptional regulatory element (PRE) sequence. In embodiments, the post-transcriptional regulatory element (PRE) sequence may be selected from a Woodchuck hepatitis virus PRE (WPRE) (such as, but not limited to wild type WPRE, such as but not limited to SEQ ID NO: 264, or a mutated WPRE, such as but not limited to WPREmut1 (SEQ ID NO: 256) or WPREmut2 (SEQ ID NO: 257)) or a hepatitis B virus (HBV) PRE (HPRE) (SEQ ID NO: 437), variant(s) thereof, or any combination thereof.

- [00226]** In embodiments, a vector may further comprise one or more promoter. In embodiments, promoter(s) may be selected from cytomegalovirus (CMV) promoter, phosphoglycerate kinase (PGK) promoter, myelin basic protein (MBP) promoter, glial fibrillary acidic protein (GFAP) promoter, modified MoMuLV LTR comprising myeloproliferative sarcoma virus enhancer (MNDU3), Ubiquitin C promoter, EF-1 alpha promoter, Murine Stem Cell Virus (MSCV) promoter, the promoter from CD69, nuclear factor of activated T-cells (NFAT) promoter, IL-2 promoter, minimal IL-2 promoter, or a combination thereof.
- [00227]** In embodiments, a vector may be a viral vector or a non-viral vector.
- [00228]** In embodiments, a vector may be selected from adenoviruses, poxviruses, alphaviruses, arenaviruses, flaviviruses, rhabdoviruses, retroviruses, lentiviruses, herpesviruses, paramyxoviruses, picornaviruses, or a combination thereof.
- [00229]** In embodiments, a vector may be pseudotyped with an envelope protein of a virus selected from the native feline endogenous virus (RD114), a chimeric version of RD114 (RD114TR), gibbon ape leukemia virus (GALV), a chimeric version of GALV (GALV-TR), amphotropic murine leukemia virus (MLV 4070A), baculovirus (GP64), vesicular stomatitis virus (VSV-G), fowl plague virus (FPV), Ebola virus (EboV), or baboon retroviral envelope glycoprotein (BaEV), lymphocytic choriomeningitis virus (LCMV), or a combination thereof.
- [00230]** In embodiments, a vector may comprise one or more Kozak sequence. In embodiments, a Kozak sequence may initiate, increase, or facilitate translation, or a combination thereof. In embodiments, the Kozak sequence may be GCCACC. In embodiments, the Kozak sequence may be ACCATGG. In embodiments, the Kozak sequence may be GCCNCCATGG, where N is a purine (A or G) (SEQ ID NO:382).
- [00231]** In embodiments, a vector may comprise one or more Factor Xa sites.
- [00232]** In embodiments, a vector may comprise one or more enhancer. In embodiments, an enhancer may comprise Conserved Non-Coding Sequence (CNS) 0, CNS 1, CNS2, CNS 3, CNS 4, or portions or any combination thereof.
- [00233]** In embodiments, the disclosure provides for one or more cells transduced with and/or expressing one or more vectors comprising nucleic acids encoding polypeptide(s).
- [00234]** In embodiments, a cell may comprise an $\alpha\beta$ T cell, a $\gamma\delta$ T cell, a natural killer cell, a natural killer T cell, a CD4⁺ T cell, CD8⁺ T cell, a CD4⁺/CD8⁺ cell, or any combination thereof.
- [00235]** In embodiments, a T cell may be a CD4⁺ T cell. In embodiments, a T cell may be a CD8⁺ T cell. In embodiments, a T cell may be a CD4⁺/CD8⁺ T cell. In embodiments, a T cell may be a $\alpha\beta$ T cell. In embodiments, a T cell may be a $\gamma\delta$ T cell.

[00236] In embodiments, a T cell may be an $\alpha\beta$ T cell and may express a CD8 polypeptide described herein. In embodiments, a CD8 polypeptide may comprise a CD8 α chain and/or a CD8 β chain, and the CD8 α chain and/or CD8 β chain may independently be modified or unmodified. In embodiments, a T cell may be an $\alpha\beta$ T cell and may express a modified CD8 polypeptide described herein, for example, a modified CD8 α polypeptide or a modified CD8 α polypeptide with a CD8 β stalk region, e.g., m1CD8 α in Constructs #11 and #12 (FIG. 4) and CD8 α^* (FIG. 55B). In embodiments, a T cell may be an $\alpha\beta$ T cell and may express one or any combination of an IL-15 polypeptide, an IL-15R α polypeptide, an IL-15/IL-15R α fusion polypeptide, a modified CD8 polypeptide, and/or a CAR.

[00237] In embodiments, a T cell may be a $\gamma\delta$ T cell and may express a CD8 polypeptide described herein. In embodiments, a CD8 polypeptide may comprise a CD8 α chain and/or a CD8 β chain, and the CD8 α chain and/or CD8 β chain may independently be modified or unmodified. In embodiments, a T cell may be a $\gamma\delta$ T cell and may express a modified CD8 polypeptide described herein, for example, a modified CD8 α polypeptide or a modified CD8 α polypeptide with a CD8 β stalk region, e.g., m1CD8 α in Constructs #11 and #12 (FIG. 4) and CD8 α^* (FIG. 55B). In embodiments, a T cell may be a $\gamma\delta$ T cell and may express one or any combination of an IL-15 polypeptide, an IL-15R α polypeptide, an IL-15/IL-15R α fusion polypeptide, a CD8 polypeptide, and/or a CAR. In embodiments, a CD8 polypeptide may comprise a CD8 α chain and/or a CD8 β chain, and the CD8 α chain and/or CD8 β chain may independently be modified or unmodified.

[00238] In embodiments, a cell or cells comprising, or comprising one or more nucleic acid(s) encoding, one or any combination of a TCR comprising an α chain and a β chain, a TCR comprising a γ chain and a δ chain, a CAR, an IL-15 polypeptide, an IL-15R α polypeptide, an IL-15/IL-15R α fusion polypeptide, and/or a CD8 polypeptide may be provided. In embodiments, a CD8 polypeptide may comprise a CD8 α chain and/or a CD8 β chain, and the CD8 α chain and/or CD8 β chain may independently be modified or unmodified.

[00239] In embodiments, a cell or cells comprising, or comprising one or more nucleic acid(s) encoding, one or any combination of a TCR comprising an α chain and a β chain, an IL-15/IL-15R α fusion polypeptide, and/or a CD8 polypeptide may be provided. In embodiments, a cell or cells comprising, or comprising one or more nucleic acid(s) encoding, one or any combination of a TCR comprising a γ chain and a δ chain, an IL-15/IL-15R α fusion polypeptide, and/or a CD8 polypeptide may be provided. In embodiments, a cell or cells comprising, or comprising one or more nucleic acid(s) encoding, one or any combination of a CAR, an IL-15/IL-15R α fusion polypeptide, and/or a CD8 polypeptide may be provided. In embodiments, a CD8 polypeptide

may comprise a CD8 α chain and/or a CD8 β chain, and the CD8 α chain and/or CD8 β chain may independently be modified or unmodified.

[00240] In embodiments, a cell or cells comprising, or comprising one or more nucleic acid(s) encoding, a TCR comprising an α chain and a β chain, an IL-15/IL-15R α fusion polypeptide, and a CD8 polypeptide may be provided. In embodiments, a cell or cells comprising, or comprising one or more nucleic acid(s) encoding, a TCR comprising a γ chain and a δ chain, an IL-15/IL-15R α fusion polypeptide, and a CD8 polypeptide may be provided. In embodiments, a cell or cells comprising, or comprising one or more nucleic acid(s) encoding, a CAR, an IL-15/IL-15R α fusion polypeptide, and a CD8 polypeptide may be provided. In embodiments, a CD8 polypeptide may comprise a CD8 α chain and/or a CD8 β chain, and the CD8 α chain and/or CD8 β chain may independently be modified or unmodified.

[00241] In embodiments, a cell or cells comprising, or comprising one or more nucleic acid(s) encoding, a TCR comprising an α chain and a β chain and an IL-15/IL-15R α fusion polypeptide may be provided. In embodiments, a cell or cells comprising, or comprising one or more nucleic acid(s) encoding, a TCR comprising a γ chain and a δ chain and an IL-15/IL-15R α fusion polypeptide may be provided. In embodiments, a cell or cells comprising, or comprising one or more nucleic acid(s) encoding, a CAR and an IL-15/IL-15R α fusion polypeptide may be provided.

[00242] In embodiments, a cell or cells comprising, or comprising one or more nucleic acid(s) encoding, a TCR comprising an α chain and a β chain and a CD8 polypeptide may be provided. In embodiments, a cell or cells comprising, or comprising one or more nucleic acid(s) encoding, a TCR comprising a γ chain and a δ chain and a CD8 polypeptide may be provided. In embodiments, a cell or cells comprising, or comprising one or more nucleic acid(s) encoding, a CAR and a CD8 polypeptide may be provided. In embodiments, a CD8 polypeptide may comprise a CD8 α chain and/or a CD8 β chain, and the CD8 α chain and/or CD8 β chain may independently be modified or unmodified.

[00243] In embodiments, one or more nucleic acid(s) may be comprised in and/or expressed from a vector or vectors.

[00244] In embodiments, a cell or cells may comprise an $\alpha\beta$ T cell, a $\gamma\delta$ T cell, a natural killer cell, a CD4 $^{+}$ T cell, CD8 $^{+}$ T cell, a CD4 $^{+}$ /CD8 $^{+}$ cell, or any combination thereof.

[00245] In embodiments, populations of cells as described herein may be provided. As a non-limiting example, the disclosure provides for a population of modified cells comprising, or comprising one or more nucleic acid(s) encoding one or any combination of an exogenous CD8 co-receptor comprising a polypeptide described herein, for example, amino acid sequences at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%,

at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 5, 7, 258, 259, 8, 9, 10, 11, 12, 13, or 14; a membrane-bound IL-15 (e.g., an IL-15/IL-15R α fusion polypeptide), as described herein; and/or a T cell receptor. In embodiments, populations of cells may comprise $\alpha\beta$ T cells, $\gamma\delta$ T cells, natural killer cells, a natural killer T cell, CD4 $^{+}$ T cells, CD8 $^{+}$ T cells, CD4 $^{+}$ /CD8 $^{+}$ cells, or any combination thereof.

[00246] In an aspect, polypeptide sequences and/or nucleic acid sequences described herein may be isolated and/or recombinant sequences.

[00247] In an aspect, cells described herein may be isolated and/or recombinant cells.

[00248] In embodiments, a method of preparing cells for immunotherapy may comprise isolating cells from a blood sample of a human subject, activating the isolated cells, transducing the activated cells with one or more vector, and expanding the transduced cells. In embodiments, a cell may comprise an $\alpha\beta$ T cell, a $\gamma\delta$ T cell, a natural killer cell, a natural killer T cell, a CD4 $^{+}$ T cell, CD8 $^{+}$ T cell, a CD4 $^{+}$ /CD8 $^{+}$ cell, or any combination thereof.

[00249] In embodiments, a method of treating a patient who has cancer may comprise administering to the patient a composition comprising the population of expanded cells, wherein the cells kill cancer cells that present a peptide in a complex with an MHC molecule on the surface, wherein the peptide is selected from SEQ ID NO: 98-255, wherein the cancer is selected from the group consisting of non-small cell lung cancer, small cell lung cancer, melanoma, liver cancer, breast cancer, uterine cancer, Merkel cell carcinoma, pancreatic cancer, gallbladder cancer, bile duct cancer, colorectal cancer, urinary bladder cancer, kidney cancer, leukemia, ovarian cancer, esophageal cancer, brain cancer, gastric cancer, prostate cancer, or a combination thereof. In embodiments, a cell may comprise an $\alpha\beta$ T cell, a $\gamma\delta$ T cell, a natural killer cell, a natural killer T cell, a CD4 $^{+}$ T cell, CD8 $^{+}$ T cell, a CD4 $^{+}$ /CD8 $^{+}$ cell, or any combination thereof. In embodiments, the composition may further comprise an adjuvant. In embodiments, the adjuvant may be selected from anti-CD40 antibody, imiquimod, resiquimod, GM-CSF, cyclophosphamide, sunitinib, bevacizumab, atezolizumab, interferon-alpha, interferon-beta, CpG oligonucleotides and derivatives, poly(I:C) and derivatives, RNA, sildenafil, particulate formulations with poly(lactide co-glycolide) (PLG), virosomes, interleukin (IL)-1, IL-2, IL-4, IL-7, IL-12, IL-13, IL-15, IL-21, IL-23, or any combination thereof.

[00250] In embodiments, a method of eliciting an immune response in a patient who has cancer may comprise administering to the patient a composition comprising the population of expanded cells, wherein the cells kill cancer cells that present a peptide in a complex with an MHC molecule on the surface, wherein the peptide is selected from SEQ ID NO: 98-255, wherein the cancer is selected from the group consisting of non-small cell lung cancer, small cell

lung cancer, melanoma, liver cancer, breast cancer, uterine cancer, Merkel cell carcinoma, pancreatic cancer, gallbladder cancer, bile duct cancer, colorectal cancer, urinary bladder cancer, kidney cancer, leukemia, ovarian cancer, esophageal cancer, brain cancer, gastric cancer, prostate cancer, or a combination thereof. In embodiments, a cell may comprise an $\alpha\beta$ T cell, a $\gamma\delta$ T cell, a natural killer cell, a natural killer T cell, a CD4⁺ T cell, CD8⁺ T cell, a CD4⁺/CD8⁺ cell, or any combination thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[00251] FIG. 1 shows a representative CD8 α subunit, *e.g.*, SEQ ID NO: 258 (CD8 α 1).

CD8 α 1 includes five domains: (1) signal peptide, (2) Ig-like domain-1, (3) a stalk region, (4) transmembrane (TM) domain, and (5) a cytoplasmic tail (Cyto) comprising a *Lck*-binding motif.

[00252] FIG. 2 shows a sequence alignment between CD8 α 1 (SEQ ID NO: 258) and m1CD8 α (SEQ ID NO: 7).

[00253] FIG. 3 shows a sequence alignment between CD8 α 2 (SEQ ID NO: 259) and m2CD8 α (SEQ ID NO: 262), in which the cysteine substitution at position 112 is indicated by an arrow.

[00254] FIG. 4 shows exemplary vectors according to an aspect of the disclosure. In embodiments, vectors may also comprise additional elements, such as those described herein, such as, but not limited to one or more promoter or one or more post-transcriptional regulatory element. In FIG. 4, the lines may represent direct linkages, with no intervening sequences, or may represent intervening sequences, such as, but not limited to, a linker, a furin, a sequence encoding a 2A polypeptide, a factor Xa site, an untranslated sequence, a translated sequence, a sequence comprising one or more restriction endonuclease sites, or a combination thereof.

[00255] FIG. 5A shows titers of viral vectors shown in FIG. 4.

[00256] FIG. 5B shows titers of further viral vectors in accordance with the present disclosure. Construct #13; Construct #14; Construct #15; Construct #16; Construct #17; Construct #18; Construct #19; Construct #21; Construct #10n; Construct #11n; and TCR: R11KEA (SEQ ID NO: 15 and SEQ ID NO: 16, which may be encoded by SEQ ID NO: 72 and SEQ ID NO: 73, respectively) (Construct #8), which binds PRAME-004 (SLLQHLIGL) (SEQ ID NO: 147). Note that Constructs #10 and #10n are different batches of the same construct (SEQ ID NO: 291 and 292) and Constructs #11 and #11n are different batches of the same construct (SEQ ID NO: 285 and 286).

[00257] FIG. 6 shows T cell manufacturing.

[00258] FIG. 7A shows expression of activation markers before and after activation in CD3⁺CD8⁺ cells.

[00259] FIG. 7B shows expression of activation markers before and after activation in CD3+CD4+ cells.

[00260] FIG. 8A shows fold expansion of cells transduced with various constructs from Donor #1. The constructs are as follows: Construct #9b; Construct #10; Construct #11; Construct #12; Construct #1; Construct #2; TCR = R11KEA.WPRE^{wt} (TCR with wild type WPRE); NT = Non-transduced T cells (as a negative control). Note that Constructs #9 and #9b are different batches of the same construct (SEQ ID NO: 287 and 288).

[00261] FIG. 8B shows fold expansion of cells transduced with various constructs from Donor #2. The constructs are as follows: Construct #9b; Construct #10; Construct #11; Construct #12; Construct #1; Construct #2; TCR = R11KEA.WPRE^{wt} (TCR with wild type WPRE) (Construct #8); NT = Non-transduced T cells (as a negative control).

[00262] FIG. 9A shows flow plots of cells transduced with Construct #9 .

[00263] FIG. 9B shows flow plots of cells transduced with Construct #10 in accordance with one embodiment of the present disclosure.

[00264] FIG. 9C shows flow plots of cells transduced with Construct #11.

[00265] FIG. 9D shows flow plots of cells transduced with Construct #12.

[00266] FIG. 10 shows % CD8+CD4+ of cells transduced with various constructs for Donor #1 and Donor #2. The constructs are as follows: Construct #9b; Construct #10; Construct #11; Construct #12; Construct #1; Construct #2; TCR = R11KEA.WPRE^{wt} TCR with wild type WPRE); NT = Non-transduced T cells (as a negative control).

[00267] FIG. 11 shows % Tet of CD8+CD4+ of cells transduced with various constructs. The constructs are as follows: Construct #9b; Construct #10; Construct #11; Construct #12; Construct #1; Construct #2; TCR = R11KEA.WPRE^{wt} (TCR with wild type WPRE); NT = Non-transduced T cells (as a negative control).

[00268] FIG. 12 shows Tet MFI (CD8+CD4+Tet+) of cells transduced with various constructs. The constructs are as follows: Construct #9b; Construct #10; Construct #11; Construct #12; Construct #1; Construct #2; TCR = R11KEA.WPRE^{wt} (TCR with wild type WPRE); NT = Non-transduced T cells (as a negative control).

[00269] FIG. 13 shows CD8 α MFI (CD8+CD4+Tet+) of cells transduced with various constructs. The constructs are as follows: Construct #9b; Construct #10; Construct #11; Construct #12; Construct #1; Construct #2; TCR = R11KEA.WPRE^{wt} (TCR with wild type WPRE); NT = Non-transduced T cells (as a negative control).

[00270] FIG. 14 shows % CD8+CD4 (of CD3+) of cells transduced with various constructs. The constructs are as follows: Construct #9b; Construct #10; Construct #11; Construct #12;

Construct #1; Construct #2; TCR = R11KEA.WPRE^{wt} (TCR with wild type WPRE); NT = Non-transduced T cells (as a negative control).

[00271] FIG. 15 shows % CD8⁺Tet⁺ (of CD3⁺) of cells transduced with various constructs. The constructs are as follows: Construct #9b; Construct #10; Construct #11; Construct #12; Construct #1; Construct #2; TCR = R11KEA.WPRE^{wt} (TCR with wild type WPRE); NT = Non-transduced T cells (as a negative control).

[00272] FIG. 16 shows Tet MFI (CD8⁺Tet⁺) of cells transduced with various constructs. The constructs are as follows: Construct #9b; Construct #10; Construct #11; Construct #12; Construct #1; Construct #2; TCR = R11KEA.WPRE^{wt} (TCR with wild type WPRE); NT = Non-transduced T cells (as a negative control).

[00273] FIG. 17 shows CD8 α MFI (CD8⁺Tet⁺) of cells transduced with various constructs. The constructs are as follows: Construct #9b; Construct #10; Construct #11; Construct #12; Construct #1; Construct #2; TCR = R11KEA.WPRE^{wt} (TCR with wild type WPRE); NT = Non-transduced T cells (as a negative control).

[00274] FIG. 18 shows % Tet⁺ (of CD3⁺) of cells transduced with various constructs. The constructs are as follows: Construct #9b; Construct #10; Construct #11; Construct #12; Construct #1; Construct #2; TCR = R11KEA.WPRE^{wt} (TCR with wild type WPRE); NT = Non-transduced T cells (as a negative control).

[00275] FIG. 19 shows VCN (upper panel) and CD3⁺Tet⁺/VCN (lower panel) of cells transduced with various constructs. The constructs are as follows: Construct #9b; Construct #10; Construct #11; Construct #12; Construct #1; Construct #2; TCR = R11KEA.WPRE^{wt} (TCR with wild type WPRE); NT = Non-transduced T cells (as a negative control).

[00276] FIGs. 20A-20C depict data showing that constructs (#10, #11, & #12) are comparable to TCR-only in mediating cytotoxicity against target positive cells lines expressing antigen at different levels (UACC257 at 1081 copies per cell and A375 at 50 copies per cell).

[00277] FIGs. 21A-21B depict data showing that IFN γ secretion in response to UACC257 is comparable among constructs, however with A375, #10 expressing is the highest among all constructs. However, comparing #9 with #11 expressing wild type and modified CD8 coreceptor sequences respectively, T cells transduced with #11 induced stronger cytokine response measured as IFN γ quantified in the supernatants from Incucyte plates. Construct #9; Construct #10; Construct #11; Construct #12; Construct #1; Construct #2; Construct #8 = R11KEA TCR only.

[00278] FIG. 22 depicts an exemplary experiment design to assess DC maturation and cytokine secretion by PBMC-derived product in response to UACC257 and A375 targets. N=2.

[00279] FIGs. 23A-23B depict data showing that the IFN γ secretion in response to A375 increases in the presence of iDCs. In the tri-cocultures with iDCs, IFN γ secretion is higher in Construct #10 compared to the other constructs. However, comparing Construct #9 with Construct #11 expressing wild type and modified CD8 coreceptor sequences respectively, T cells transduced with #11 induced stronger cytokine response measured as IFN γ quantified in the culture supernatants of three-way cocultures using donor D600115, E:T:iDC::1:1/10:1/4. Construct #9; Construct #10; Construct #11; Construct #12; Construct #1; Construct #2; Construct #8 = R11KEA TCR only.

[00280] FIGs. 24A-24B depict data showing that IFN γ secretion in response to A375 increases in the presence of iDCs. In the tri-cocultures with iDCs, IFN γ secretion was higher in Construct #10 compared to the other constructs. IFN γ quantified in the culture supernatants of three-way cocultures using donor D150081, E:T:iDC::1:1/10:1/4. Construct #9; Construct #10; Construct #11; Construct #12; Construct #1; Construct #2; Construct #8 = R11KEA TCR only.

[00281] FIGs. 25A-25B depict data showing that IFN γ secretion in response to UACC257 increases in the presence of iDCs. In the tri-cocultures with iDCs, IFN γ secretion is higher in Construct #10 compared to the other constructs. However, comparing Construct #9 with Construct #11 expressing wild type and modified CD8 coreceptor sequences respectively, T cells transduced with Construct #11 induced stronger cytokine response measured as IFN γ quantified in the culture supernatants of three-way cocultures using donor D600115, E:T:iDC::1:1/10:1/4. Construct #9; Construct #10; Construct #11; Construct #12; Construct #1; Construct #2; Construct #8 = R11KEA TCR only.

[00282] FIG. 26 shows T cell manufacturing in accordance with one embodiment of the present disclosure.

[00283] FIG. 27A shows expression of activation markers before and after activation in CD3+CD8+ cells.

[00284] FIG. 27B shows expression of activation markers before and after activation in CD3+CD4+ cells in accordance with one embodiment of the present disclosure.

[00285] FIG. 28 shows fold expansion of cells transduced with various constructs.

[00286] FIGs. 29A-29B show % CD8+CD4+ of cells transduced with various constructs in accordance with one embodiment of the present disclosure.

[00287] FIGs. 30A-30B show % Tet of CD8+CD4+ of cells transduced with various constructs in accordance with one embodiment of the present disclosure.

[00288] FIGs. 31A-31B show Tet MFI (CD8+CD4+Tet+) of cells transduced with various constructs in accordance with one embodiment of the present disclosure.

- [00289]** FIGs. 32A-32B show % CD8+CD4- (of CD3+) of cells transduced with various constructs in accordance with one embodiment of the present disclosure.
- [00290]** FIGs. 33A-33B show % CD8+Tet+ (of CD3+) of cells transduced with various constructs in accordance with one embodiment of the present disclosure.
- [00291]** FIGs. 34A-34B show Tet MFI (CD8+Tet+) of cells transduced with various constructs in accordance with one embodiment of the present disclosure.
- [00292]** FIGs. 35A-35B show % Tet+ (of CD3+) of cells transduced with various constructs in accordance with one embodiment of the present disclosure.
- [00293]** FIGs. 36A-36B show VCN of cells transduced with various constructs in accordance with one embodiment of the present disclosure.
- [00294]** FIG. 37 shows T cell manufacturing in accordance with one embodiment of the present disclosure.
- [00295]** FIG. 38 shows % Tet of CD8+CD4+ of cells transduced with various constructs.
- [00296]** FIG. 39 shows Tet MFI of CD8+CD4+Tet+ of cells transduced with various constructs.
- [00297]** FIG. 40 shows Tet MFI of CD8+Tet+ of cells transduced with various constructs.
- [00298]** FIG. 41 shows % Tet+ of CD3+ cells transduced with various constructs.
- [00299]** FIG. 42 shows vector copy number (VCN) of cells transduced with various constructs.
- [00300]** FIG. 43 shows the % T cell subsets in cells transduced with various constructs. FACS analysis was gated on CD3+TCR+.
- [00301]** FIGs. 44A-44B show % T cell subsets in cells transduced with various constructs. FACS analysis was gated on CD4+CD8+ for FIG. 44A and on CD4-CD8+TCR+ for FIG. 44B.
- [00302]** FIGs. 45A-45B depict data showing that Constructs #13 and #10 are comparable to TCR-only in mediating cytotoxicity against UACC257 target positive cells lines expressing high levels of antigen (1081 copies per cell). Construct # 15 was also effective but slower in killing compared to Constructs #13 and #10. The effector:target ratio used to generate these results was 4:1.
- [00303]** FIG. 46 shows IFN γ secretion in response in UACC257 cell line was higher with Construct #13 compared to Construct #10. IFN γ quantified in the supernatants from Incucyte plates. The effector:target ratio used to generate these results was 4:1.
- [00304]** FIG. 47 shows ICI marker frequency (2B4, 41BB, LAG3, PD-1, TIGIT, TIM3, CD39+CD69+, and CD39-CD69-).

[00305] FIGs. 48A–48G show increased expression of IFN γ , IL-2, and TNF α with CD4+CD8+ cells transduced with Construct #10 (WT signal peptide, CD8 β 1) compared to other constructs. FACS analysis was gated on CD3+CD4+CD8+ cells against UACC257, 4:1 E:T.

[00306] FIGs. 49A–49G show increased expression of IFN γ , IL-2, MIP-1 β , and TNF α with CD4-CD8+ cells transduced with Construct #10 (WT signal peptide, CD8 β 1) compared to other constructs. FACS analysis was gated on CD3+CD4-CD8+ cells against UACC257, 4:1 E:T.

[00307] FIGs. 50A–50G show increased expression of IL-2 and TNF α with CD3+TCR+ cells transduced with Construct #10 (WT signal peptide, CD8 β 1) compared to other constructs. FACS analysis was gated on CD3+TCR+ cells against UACC257, 4:1 E:T.

[00308] FIGs. 51A–51C show results from FACS analysis gated on CD4+CD8+ cells against A375, 4:1 E:T.

[00309] FIGs. 52A–52C show results from FACS analysis gated on CD4-CD8+ cells against A375, 4:1 E:T.

[00310] FIGs. 53A–53C show results from FACS analysis gated on CD3+TCR+ cells against A375, 4:1 E:T.

[00311] FIG. 54 shows T cell manufacturing in accordance with one embodiment of the present disclosure.

[00312] FIGs. 55A–55C show interaction between peptide/MHC complex of antigen-presenting cell (APC) with T cell by binding a complex of TCR and CD8 $\alpha\beta$ heterodimer (FIG. 55A, e.g., produced by transducing T cells with Constructs #2, #3, #4, #10, #13, #14, #15, #16, #17, #18, or #21), a complex of TCR and homodimer CD8 α having its stalk region replaced with CD8 β stalk region (CD8 $\alpha\alpha^*$) (FIG. 55B, e.g., produced by transducing T cells with Construct #11, #12, or #19), and a complex of TCR and CD8 α homodimer (FIG. 55C, e.g., produced by transducing T cells with Constructs #1, #5, #6, #7, or #9).

[00313] FIG. 56 shows the levels of IL-12 secretion by dendritic cells (DC) in the presence of CD4+ T cells transduced with Construct #10 or #11 and immature dendritic cells (iDCs) in accordance with one embodiment of the present disclosure.

[00314] FIG. 57 shows the levels of TNF- α secretion by dendritic cells (DC) in the presence of CD4+ T cells transduced with Construct #10 or #11 and immature dendritic cells (iDCs) in accordance with one embodiment of the present disclosure.

[00315] FIG. 58 shows the levels of IL-6 secretion by dendritic cells (DC) in the presence of CD4+ T cells transduced with Construct #10 or #11 and immature dendritic cells (iDCs) in accordance with one embodiment of the present disclosure.

[00316] FIG. 59 shows a scheme of determining the levels of cytokine secretion by dendritic cells (DC) in the presence of PBMCs transduced with various constructs and target cells in accordance with one embodiment of the present disclosure.

[00317] FIG. 60 shows the levels of IL-12 secretion by dendritic cells (DC) in the presence of PBMCs transduced with various constructs and target cells in accordance with one embodiment of the present disclosure.

[00318] FIG. 61 shows the levels of TNF- α secretion by dendritic cells (DC) in the presence of PBMCs transduced with various constructs and target cells in accordance with one embodiment of the present disclosure

[00319] FIG. 62 shows the levels of IL-6 secretion by dendritic cells (DC) in the presence of PBMCs transduced with various constructs and target cells in accordance with one embodiment of the present disclosure.

[00320] FIGs. 63A-63C show IFN γ production from the transduced CD4⁺ selected T cells obtained from Donor #1 (FIG. 63A), Donor #2 (FIG. 63B), and Donor #3 (FIG. 63C) in accordance to one embodiment of the present disclosure.

[00321] FIG. 63D shows EC50 values (ng/ml) in FIG. 63A-63C.

[00322] FIGs. 64A-64C show IFN γ production from the transduced PBMC obtained from Donor #4 (FIG. 64A), Donor #1 (FIG. 64B), and Donor #3 (FIG. 64C) and their respective EC50 values (ng/ml) in accordance to one embodiment of the present disclosure.

[00323] FIG. 64D shows comparison of EC50 values (ng/ml) among different donors in FIG. 64A-64C.

[00324] FIGs. 65A-65C show IFN γ production from the transduced PBMC (FIG. 65A), CD8⁺ selected T cells (FIG. 65B), and CD4⁺ selected T cells (FIG. 65C) and their respective EC50 values (ng/ml) from a single donor in accordance to one embodiment of the present disclosure.

[00325] FIG. 66 schematically depicts an exemplary membrane-bound IL-15 bound to the membrane of a T cell, which may be provided in embodiments. In embodiments membrane-bound IL-15 may signal via an intermediate IL-2/IL-15 receptor, as a non-limiting example.

[00326] FIG. 67A depicts an exemplary membrane-bound IL-15 polypeptide in which an IL-15 polypeptide is located N-terminal to an IL-15R α polypeptide, which may be provided In embodiments.

[00327] FIG. 67B depicts an exemplary membrane-bound IL-15 polypeptide in which an IL-15 polypeptide is located C-terminal to an IL-15R α polypeptide, which may be provided In embodiments. Nucleic acids encoding such constructs are also provided, in embodiment. In FIG. 67A and 67B, L represents one or more optional linker, and the lines may represent direct linkages, with no intervening sequences, or may represent intervening sequences, such as, but

not limited to, a linker, an untranslated sequence (in the case of a nucleic acid sequence), a translated sequence, a sequence comprising one or more restriction endonuclease sites (in the case of a nucleic acid sequence), or a combination thereof.

[00328] FIG. 68A depicts an exemplary membrane-bound IL-15 polypeptide in which an IL-15 polypeptide is located N-terminal to an IL-15R α polypeptide, and a signal peptide (SP) is located N terminal to the IL-15 polypeptide, which may be provided in embodiments.

[00329] FIG. 68B depicts an exemplary membrane-bound IL-15 polypeptide in which an IL-15 polypeptide is located C-terminal to an IL-15R α polypeptide, and a signal peptide (SP) is located N terminal to the IL-15R α polypeptide, which may be provided in embodiments. Nucleic acids encoding such constructs are also provided, in embodiments. In FIG. 68A and 68B, L represents one or more optional linker, and the lines may represent direct linkages, with no intervening sequences, or may represent intervening sequences, such as, but not limited to, a linker, an untranslated sequence (in the case of a nucleic acid sequence), a translated sequence, a sequence comprising one or more restriction endonuclease sites (in the case of a nucleic acid sequence), or a combination thereof.

[00330] FIG. 69A depicts exemplary polypeptide constructs, which may be provided in embodiments.

[00331] FIG. 69B depicts exemplary nucleic acid constructs, which may be provided in embodiments. In FIG. 69A and 69B, the lines may represent direct linkages, with no intervening sequences, or may represent intervening sequences, such as, but not limited to, a linker, an untranslated sequence (in the case of a nucleic acid sequence), a translated sequence, a sequence comprising one or more restriction endonuclease sites (in the case of a nucleic acid sequence), or a combination thereof.

[00332] FIG. 70 depicts exemplary vector constructs, which may be provided in embodiments. In embodiments, vectors may also comprise additional elements, such as those described herein, such as, but not limited to one or more promoter or one or more post-transcriptional regulatory element. In FIG. 70, the lines may represent direct linkages, with no intervening sequences, or may represent intervening sequences, such as, but not limited to, a linker, a furin, a sequence encoding a 2A polypeptide, a factor Xa site, an untranslated sequence, a translated sequence, a sequence comprising one or more restriction endonuclease sites, or a combination thereof.

[00333] FIGs. 71A-71D show %TCR⁺ (A), % IL15R α +TCR⁺(B), fold expansion (C) and cell viability (D) of different vector constructs co-expressing TCR and mbIL15 (Alt v1-v4, v7) compared to TCR only ("TCR") and non-transduced cells ("NT") as control in an exemplary assay. The flow cytometer was gated on CD8⁺. Data are grouped (n=2) and represented as mean.

[00334] FIGs. 72A-72D show %TCR+ (A), % IL15 α +TCR+(B), fold expansion (C) and total TCR+ cells (D) of different vector constructs co-expressing TCR and mbIL15 (Alt v1-v4, v7) compared to TCR only ("TCR") and non-transduced cells ("NT") as control in an exemplary assay. The flow cytometer was gated off CD8+. Data are grouped (n=4) and represented as mean.

[00335] FIGs. 73A-73C show exemplary kinetic killing (A), tumor growth indices (B) and IFN γ release (C) in a co-culture assay of UACC257 tumor cells expressing red fluorescent protein (RFP) ("UACC257-RFP") with non-transduced ("NT") cells, cells transduced with TCR only ("TCR") or cells transduced with various constructs co-expressing TCR and mbIL15 (Alt v1-v4, v7). Cells were challenged with UACC257 cells four times over 9-10 days at about 0 hours, about 70 hours, about 120 hours, and about 170 hours, at an effector:target ratio of 1:1. UACC257-RFP cells alone were assayed as a control. The data are grouped (n=4), represented as mean, and TCR+ normalized. Data were gathered using IncuCyte and ELISA.

[00336] FIGs. 74A-74C show exemplary kinetic killing (A), tumor growth indices (B) and IFN γ release (C) in a co-culture assay of hs695T tumor cells expressing red fluorescent protein (RFP) ("hs695T-RFP") with non-transduced ("NT") cells, cells transduced with TCR only ("TCR") or cells transduced with various constructs co-expressing TCR and mbIL15 (Alt v1-v4, v7). Cells were challenged with hs695T cells four times over 9-10 days at about 0 hours, about 70 hours, about 120 hours, and about 170 hours at an effector:target ratio of 2:1. hs695T-RFP cells alone were assayed as a control. The data are grouped (n=4), represented as mean, and TCR+ normalized. Data were gathered using IncuCyte and ELISA.

[00337] FIGs. 75A-75C show exemplary kinetic killing (A), tumor growth indices (B) and IFN γ release (C) in a co-culture assay of A375 tumor cells expressing red fluorescent protein (RFP) ("A375 -RFP") with non-transduced ("NT") cells, cells transduced with TCR only ("TCR") or cells transduced with various constructs. Cells were challenged with A375 cells four times over 9-10 days at about 0 hours, about 70 hours, about 120 hours, and about 170 hours at an effector:target ratio of 4:1. A375-RFP cells alone were assayed as a control. The data are grouped (n=4), represented as mean, and TCR+ normalized. Data were gathered using IncuCyte and ELISA.

[00338] FIGs. 76A-76D show the percentage of TemRA, Tem, T naïve/scm, and Tcm cells, of cells transduced with TCR only ("TCR") and various constructs in an example. Non-transduced cells ("NT") were assayed as a control. The panel in FIG. 76A was performed on cells that were not exposed to antigen-presenting tumor cells (pre-Ag). The panels in FIG. 76B-D were performed after four tumor stimulations with UACC257 cells (B), hs695T cells (C) and A375

cells (D) over 9-10 days. The flow cytometer was gated on CD3+CD8+ cells. Data are represented as mean.

[00339] FIGs. 77A-77D show the percentage of CD8+ cells that were positive for each of LAG-3, PD-1, TIGIT, TIM-3, CD39, and CD69 prior to (A) or after exposure of the cells to antigen-bearing UACC257 cells (B), hs695T cells (C) or A375 cells (D) in an example. Cells were challenged four times with tumor cells over 9-10 days. Expression percentages are shown by each of non-transduced ("NT") cells and cells transduced with TCR only ("TCR"), and cells transduced with various constructs. Data are grouped (n=4) and are represented as mean.

[00340] FIGs. 78A-78F show flow plots of cells transduced with TCR only ("TCR") and various constructs in an example. Non-transduced cells ("NT") were assayed as a control. X-axis shows staining for cell viability markers (Helix NP), Y axis shows staining for apoptosis markers (ApoTrackerTM). Flow plots were performed on cells after four antigen challenges over 9-10 days with antigen-presenting UACC257 tumor cells.

[00341] FIGs. 78G-78H show frequencies of live and dead apoptotic cells, respectively. Cells with similar results were obtained after challenges with hs695T and A375 tumor cells (data not shown). The flow cytometer was gated on CD8+ cells. Data are grouped (n=4) and represented as mean.

[00342] FIGs. 79A-79C show proliferation indices of cells transduced with TCR only ("TCR") and various constructs. Cells were challenged twice with UACC257 tumor cells (A), hs695T tumor cells (B) or A375 tumor cells (C) over 6 days. The flow cytometer was gated on CD8+ cells. Data are grouped (n=4) and represented as mean.

[00343] FIGs. 80A-80C show total cell count (A), fold expansion (B) and cell viability (C) of cells transduced with TCR only ("TCR") and various constructs in the absence or presence of exogenous Interleukin-7 and Interleukin-15 ("IL7/15") and in the absence of antigen stimulation. Conditions with exogenous Interleukin-7 and Interleukin-15 ("IL7/15") were terminated on day 17 while conditions without exogenous Interleukin-7 and Interleukin-15 ("IL7/15") were in culture up to 31 days. Data are grouped (n=4) and represented as mean.

[00344] FIGs. 81A-81B show exemplary kinetic killing of cells transduced with various constructs after 31 days in culture without exogenous cytokine addition or antigen stimulation. To assess the killing capacities, transduced cells were co-cultured with UACC257 tumor cells at an effector:target ratio of 1:1 (A) or hs695T tumor cells at an effector:target ratio of 2:1 (B). Data are grouped (n=4), represented as mean, and TCR+ normalized.

DETAILED DESCRIPTION**Membrane-Bound IL-15**

[00345] In embodiments a membrane-bound IL-15 polypeptide (membrane-bound IL-15 or mbIL-15) is provided. In embodiments nucleic acids described herein comprise and/or encode a membrane-bound IL-15 polypeptide. In embodiments vectors described herein comprise and/or encode a membrane-bound IL-15 polypeptide. In embodiments cells described herein comprise and/or express a membrane-bound IL-15 polypeptide. In embodiments compositions described herein comprise a membrane-bound IL-15 polypeptide or comprise cells comprising and/or expressing a membrane-bound IL-15 polypeptide. In embodiments IL-15 is rendered membrane-bound by expressing an IL-15 polypeptide and an IL-15R α polypeptide in an IL-15/IL-15R α fusion polypeptide (IL-15/IL-15R α).

[00346] Membrane-bound IL-15 polypeptides are provided. Isolated nucleic acid sequences comprising one or more nucleic acid sequences encoding one or more membrane-bound IL-15 polypeptides are provided. Vectors comprising one or more nucleic acid sequences comprising one or more nucleic acid sequences encoding one or more membrane-bound IL-15 polypeptides are provided. Cells comprising and/or expressing one or more membrane-bound IL-15 polypeptides are provided. Cells comprising or expressing one or more nucleic acid sequences comprising one or more nucleic acid sequences encoding one or more membrane-bound IL-15 polypeptides are provided. Cells comprising or expressing one or more vectors comprising one or more nucleic acid sequences comprising one or more nucleic acid sequences encoding one or more membrane-bound IL-15 polypeptides are provided. In embodiments, cells described herein may comprise a membrane-bound IL-15 polypeptide, a CD8 polypeptide, a cell receptor (TCR) comprising an α chain and a β chain, a TCR comprising an γ chain and a δ chain, a chimeric antigen receptor (CAR), or any combination thereof. In embodiments a cell may comprise an $\alpha\beta$ T cell, an $\gamma\delta$ T cell, a natural killer cell, a natural killer T cell, a CD4⁺ cell, a CD8⁺ cell, a CD4⁺/CD8⁺ cell, or any combination thereof. In embodiments such polypeptides, nucleic acids, vectors, and/or cells may be isolated, recombinant, and/or engineered. Compositions comprising such polypeptides, nucleic acids, vectors, and/or cells are provided.

[00347] In an aspect, polypeptide sequences and/or nucleic acid sequences described herein may be isolated and/or recombinant sequences.

[00348] In an aspect, cells described herein may be isolated and/or recombinant cells.

[00349] Membrane-bound IL-15 may comprise, for example, an IL-15/IL-15R α fusion polypeptide and/or an IL-15R α /IL-15 fusion polypeptide. One or more linkers may be disposed between IL-15 and IL-15R α or between IL-15R α and IL-15. In embodiments an IL-15 polypeptide is located N-terminal to an IL-15R α polypeptide in a membrane-bound IL-15

polypeptide. (FIG. 67A). In embodiments, an IL-15 polypeptide is located C-terminal to an IL-15R α polypeptide in a membrane-bound IL-15 polypeptide. (FIG. 67B). The IL-15 polypeptide in FIGS. 67A and 67B may be immature wild type, immature mutated, mature wild type, or mature mutated. The IL-15R α polypeptide in FIGS. 67A and 67B may be immature wild type, immature mutated, mature wild type, or mature mutated. In embodiments the IL-15 polypeptide in FIG. 67A and FIG. 67B is mature and may or may not be mutated, and the IL-15R α polypeptide in FIG. 67A and FIG. 67B is mature and may or may not be mutated. In embodiments the IL-15 polypeptide in FIG. 67A and FIG. 67B is mature and may or may not be mutated, and the IL-15R α polypeptide in FIG. 67A and FIG. 67B is mature and mutated. Although a linker is depicted in FIGS. 67A and 67B, a mbIL-15 may or may not comprise a linker.

[00350] In embodiments an IL-15 polypeptide and an IL-15R α polypeptide is linked by one or more linker. An IL-15/IL-15R α fusion polypeptide and/or an IL-15R α /IL-15 fusion polypeptide may also comprise one or more linker. In embodiments a membrane-bound IL-15 comprises and/or is encoded by a structure as shown in FIG. 67A or FIG. 67B. In FIGS. 67A and 67B, the lines connecting the IL-15 to the one or more linker (L) and the one or more linker (L) to the IL-15R α may represent direct linkages, with no intervening sequences, or may represent intervening sequences, such as, but not limited to, a linker, an untranslated sequence (in the case of a nucleic acid sequence), a translated sequence, a sequence comprising one or more restriction endonuclease sites (in the case of a nucleic acid sequence), or a combination thereof.

[00351] In embodiments IL-15/IL-15R α fusion polypeptide and/or an IL-15R α /IL-15 fusion polypeptide may comprise one or more signal peptide. In embodiments a membrane-bound IL-15 comprising one or more signal peptide and, optionally, one or more linkers may comprise and/or be encoded by a structure as shown in FIG. 68A or FIG. 68B. An exemplary IL-15/IL-15R α fusion polypeptide comprising, optionally, at least one linker and at least one signal peptide is depicted in FIG. 68A. An exemplary IL-15R α /IL-15 fusion polypeptide comprising, optionally, at least one linker and at least one signal peptide is depicted in FIG. 68B. The IL-15 polypeptide in FIGS. 68A and 68B may be immature wild type, immature mutated, mature wild type, or mature mutated. The IL-15R α polypeptide in FIGS. 68A and 68B may be immature wild type, immature mutated, mature wild type, or mature mutated. In embodiments the IL-15 polypeptide in FIG. 68A and FIG. 68B is mature and may or may not be mutated, and the IL-15R α polypeptide in FIG. 68A and FIG. 68B is mature and may or may not be mutated. In embodiments the IL-15 polypeptide in FIG. 68A and 68B is mature and may or may not be mutated, and the IL-15R α polypeptide in FIG. 68A and 68B is mature and mutated. In FIGS. 68A and 68B, the lines connecting (a) the one or more signal peptide (SP) to the IL-15, the IL-15

to the one or more linker (L), and the one or more linker to the IL-15R α (as in FIG. 68A) or (b) the one or more signal peptide (SP) to the IL-15 α , the IL-15 α to the one or more linker (L), and the one or more linker to the IL-15 (as in FIG. 68B) may represent direct linkages, with no intervening sequences, or may represent intervening sequences, such as, but not limited to, a linker, an untranslated sequence (in the case of a nucleic acid sequence), a translated sequence, a sequence comprising one or more restriction endonuclease sites (in the case of a nucleic acid sequence), or a combination thereof.

[00352] In embodiments an IL-15/IL-15R α fusion polypeptide comprises an entire IL-15 polypeptide, an entire IL-15R α polypeptide, or both. In embodiments an entire, or full, wild type IL-15 polypeptide may comprise SEQ ID NO: 305. In embodiments an entire, or full, wild type IL-15R α polypeptide may comprise SEQ ID NO: 306.

[00353] In embodiments an IL-15/IL-15R α fusion polypeptide comprises a mature IL-15 polypeptide (e.g., SEQ ID NO: 307), a mature IL-15R α polypeptide (e.g., SEQ ID NO: 309), which may be mutated (e.g., SEQ ID NO: 311, 313, 315), or both. In embodiments a mature wild type IL-15 polypeptide may comprise or consist of SEQ ID NO: 307 or may comprise or consist of amino acids 49-162 of SEQ ID NO: 305. In embodiments a mature wild type IL-15R α polypeptide may comprise or consist of SEQ ID NO: 309 or may comprise or consist of amino acids 31-267 of SEQ ID NO: 306. In embodiments a mature wild type IL-15 polypeptide is encoded by a nucleic acid comprising or consisting of the nucleic acid set forth in SEQ ID NO: 308. In embodiments a mature wild type IL-15R α polypeptide is encoded by a nucleic acid comprising or consisting of the nucleic acid set forth in SEQ ID NO: 310. However, In embodiments an IL-15/IL-15R α fusion polypeptide does not comprise a mature wild type IL-15R α as in SEQ ID NO: 309 or sequences having about 95% or more sequence identity thereto. In embodiments an IL-15/IL-15R α fusion polypeptide does not comprise a mature wild type IL-15R α encoded by SEQ ID NO: 310 or sequences having about 80%, about 85%, about 90%, or about 95% or more sequence identity thereto.

[00354] In embodiments an IL-15 polypeptide is mutated and/or truncated, an IL-15R α polypeptide is mutated and/or truncated, or both are mutated and/or truncated.

[00355] In embodiments an IL-15 polypeptide may comprise or may lack a native signal peptide (which may have a sequence comprising SEQ ID NO: 369), may comprise or may lack a native propeptide (which may have a sequence comprising SEQ ID NO: 371), or any combination thereof.

[00356] In embodiments an IL-15R α polypeptide may comprise or may lack a native signal sequence (which may have a sequence comprising SEQ ID NO: 370).

[00357] In embodiments an IL-15R α polypeptide, which may be a mature IL-15R α polypeptide (e.g., SEQ ID NO: 309), may be mutated. In embodiments an IL-15R α polypeptide IL-15R α polypeptide, may comprise a mutated transmembrane domain. In embodiments the transmembrane domain of an IL-15R α polypeptide may comprise or consist of SEQ ID NO: 376 or SEQ ID NO: 378. In embodiments the transmembrane domain of an IL-15R α polypeptide may be encoded by a nucleic acid comprising or consisting of the sequence set forth in SEQ ID NO: 377 or SEQ ID NO: 379. In embodiments a mutant IL-15R α may comprise a heterologous transmembrane domain. In embodiments, a heterologous transmembrane domain may be derived from CD25. In embodiments a transmembrane domain derived from CD25 comprises or consists of SEQ ID NO: 372 or a sequence having at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identity thereto. In embodiments a transmembrane domain derived from CD25 is encoded by a nucleic acid comprising or consisting of the nucleic acid seq forth in SEQ ID NO: 373 or a sequence having at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identity thereto. In embodiments, an IL-15R α polypeptide comprising a CD25 transmembrane domain comprises or consists of the sequence set forth in SEQ ID NO: 311 or a sequence having at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identity thereto. In embodiments, an IL-15R α polypeptide comprising a CD25 transmembrane domain is encoded by a nucleic acid comprising or consisting of the sequence set forth in SEQ ID NO: 312 or a sequence having at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identity thereto. In embodiments, a heterologous transmembrane domain may be derived from CD28. In embodiments a transmembrane domain derived from CD28 comprises or consists of SEQ ID NO: 374 or a sequence having at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identity thereto. In embodiments a transmembrane domain derived from CD28 is encoded by a nucleic acid comprising or consisting of the nucleic acid seq forth in SEQ ID NO: 375 or a sequence having at least about 80%, at least about 85%, at least about 90%, at least about 91%,

at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identity thereto. In embodiments, an IL-15R α polypeptide comprising a CD28 transmembrane domain comprises or consists of the sequence set forth in SEQ ID NO: 313 or a sequence having at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identity thereto. In embodiments, an IL-15R α polypeptide comprising a CD28 transmembrane domain is encoded by a nucleic acid comprising or consisting of the sequence set forth in SEQ ID NO: 314 or a sequence having at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identity thereto. In embodiments an IL-15R α may be mutated by deleting exon 3 of human IL-15R α genomic DNA. In embodiments, an IL-15R α polypeptide comprising a deletion of exon 3 comprises or consists of the sequence set forth in SEQ ID NO: 315 or a sequence having at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identity thereto. In embodiments, an IL-15R α polypeptide comprising a deletion of exon 3 is encoded by a nucleic acid comprising or consisting of the sequence set forth in SEQ ID NO: 316 or a sequence having at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identity thereto. In embodiments, function(s) of IL-15R α , such as, but not limited to, the ability of IL-15R α be membrane-bound and one or more signaling function(s) of IL-15 α are preserved and/or enhanced in an IL-15R α polypeptide having a heterologous transmembrane domain or deleted exon 3.

[00358] In embodiments the disclosure provides for nucleic acids encoding polypeptide(s) described herein.

[00359] In an aspect, polypeptide sequences and/or nucleic acid sequences described herein may be isolated and/or recombinant sequences.

[00360] In an aspect, cells described herein may be isolated and/or recombinant cells.

[00361] In embodiments an IL-15 polypeptide has a sequence comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the amino acid sequence of

SEQ ID NO: 305. In embodiments, function(s) of IL-15, such as, but not limited to, one or more signaling function(s) of IL-15, are preserved and/or enhanced in a mutated IL-15 polypeptide.

[00362] In embodiments an IL-15 polypeptide has a sequence comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the amino acid sequence of SEQ ID NO: 307. In embodiments, function(s) of IL-15, such as, but not limited to, one or more signaling function(s) of IL-15, are preserved and/or enhanced in a mutated IL-15 polypeptide.

[00363] In embodiments an IL-15 polypeptide comprises (a) SEQ ID NO: 305 comprising one, two, three, four, or five amino acid substitutions or (b) SEQ ID NO: 307 comprising one, two, three, four, or five amino acid substitutions. In embodiments, amino acid substitutions are conservative or non-conservative. In embodiments amino acid substitution(s) are conservative amino acid substitution(s). In embodiments, function(s) of IL-15, such as, but not limited to, one or more signaling function(s) of IL-15, are preserved and/or enhanced in a mutated IL-15 polypeptide.

[00364] In embodiments an IL-15 polypeptide is encoded by a nucleic acid comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the nucleic acid of SEQ ID NO: 308. In embodiments, function(s) of IL-15, such as, but not limited to, one or more signaling function(s) of IL-15, are preserved and/or enhanced in an IL-15 polypeptide encoded by a mutated nucleic acid sequence.

[00365] In embodiments an IL-15 polypeptide is encoded by a nucleic acid comprising (a) SEQ ID NO: 308 comprising one, two, three, four, or five nucleic acid substitutions. In embodiments, one or more nucleic acid substitution in a codon may result in a codon encoding the same amino acid or may result in a codon encoding a different amino acid. In embodiments, one or more nucleic acid substitution in a codon may result in a codon encoding a conservative amino acid substitution. In embodiments, one or more nucleic acid substitution in a codon may result in a codon encoding the same amino acid. In embodiments, function(s) of IL-15, such as, but not limited to, one or more signaling function(s) of IL-15, are preserved and/or enhanced in an IL-15 polypeptide encoded by a mutated nucleic acid sequence.

[00366] In embodiments, a nucleic acid encoding an IL-15 polypeptide may comprise a stop codon (such as TAA, TAG, or TGA), positioned at, as a non-limiting example, at the 3' end of a nucleotide encoding an IL-15 polypeptide.

[00367] In embodiments an IL-15R α polypeptide has a sequence comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the amino acid sequence of SEQ ID NO: 306. In embodiments an IL-15R α polypeptide has a sequence comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the amino acid sequence of SEQ ID NO: 309. However, In embodiments an IL-15R α polypeptide does not have a sequence comprising or consisting of SEQ ID NO: 309 or a sequence having about 95% or more sequence identity thereto. In embodiments an IL-15R α polypeptide has a sequence comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the amino acid sequence of SEQ ID NO: 311. In embodiments an IL-15R α polypeptide has a sequence comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the amino acid sequence of SEQ ID NO: 313. In embodiments an IL-15R α polypeptide has a sequence comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the amino acid sequence of SEQ ID NO: 315. In embodiments, function(s) of IL-15R α , such as, but not limited to, the ability of IL-15R α be membrane-bound and one or more signaling function(s) of IL-15 α are preserved and/or enhanced in a mutated IL-15R α polypeptide.

[00368] In embodiments an IL-15R α polypeptide may comprise (a) SEQ ID NO: 306 comprising one, two, three, four, or five amino acid substitutions; (b) SEQ ID NO: 309 comprising one, two, three, four, or five amino acid substitutions; (c) SEQ ID NO: 311 comprising one, two, three, four, or five amino acid substitutions; (d) SEQ ID NO: 313 comprising one, two, three, four, or five amino acid substitutions; or (e) SEQ ID NO: 315 comprising one, two, three, four, or five amino acid substitutions. However, In embodiments an IL-15R α polypeptide does not have a sequence comprising or consisting of SEQ ID NO: 309 or a sequence having about 95% or more sequence identity thereto. In embodiments, amino acid substitutions are conservative or non-conservative. In embodiments amino acid substitution(s)

are conservative amino acid substitution(s). In embodiments, function(s) of IL-15R α , such as, but not limited to, the ability of IL-15R α be membrane-bound and one or more signaling function(s) of IL-15 α are preserved and/or enhanced in a mutated IL-15R α polypeptide.

[00369] In embodiments an IL-15R α polypeptide is encoded by a nucleic acid comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the nucleic acid of SEQ ID NO: 310. However, In embodiments an IL-15R α polypeptide is not encoded by a nucleic acid comprising SEQ ID NO: 310 or a having about 85%, about 90%, about 95% or more sequence identity thereto. In embodiments an IL-15R α polypeptide is encoded by a nucleic acid comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the nucleic acid of SEQ ID NO: 312. In embodiments an IL-15R α polypeptide is encoded by a nucleic acid comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the nucleic acid of SEQ ID NO: 314. In embodiments an IL-15R α polypeptide is encoded by a nucleic acid comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the nucleic acid of SEQ ID NO: 316. In embodiments, function(s) of IL-15R α , such as, but not limited to, the ability of IL-15R α be membrane-bound and one or more signaling function(s) of IL-15 α are preserved and/or enhanced in an IL-15 α polypeptide encoded by a mutated nucleic acid sequence.

[00370] In embodiments an IL-15R α polypeptide is encoded by a nucleic acid comprising (a) SEQ ID NO: 310 comprising one, two, three, four, or five nucleic acid substitutions; (b) SEQ ID NO: 312 comprising one, two, three, four, or five nucleic acid substitutions; (c) SEQ ID NO: 314 comprising one, two, three, four, or five nucleic acid substitutions, and (d) SEQ ID NO: 316 comprising one, two, three, four, or five nucleic acid substitutions. However, In embodiments an IL-15R α polypeptide is not encoded by a nucleic acid comprising SEQ ID NO: 310 or a having about 85%, about 90%, about 95% or more sequence identity thereto. In embodiments, one or more nucleic acid substitution in a codon may result in a codon encoding the same amino acid or may result in a codon encoding a different amino acid. In embodiments, one or more nucleic acid substitution in a codon may result in a codon encoding a conservative amino acid substitution. In

embodiments, one or more nucleic acid substitution in a codon may result in a codon encoding the same amino acid. In embodiments, function(s) of IL-15R α , such as, but not limited to, the ability of IL-15R α be membrane-bound and one or more signaling function(s) of IL-15 α are preserved and/or enhanced in an IL-15 α polypeptide encoded by a mutated nucleic acid sequence.

[00371] In embodiments, a nucleic acid encoding an IL-15R α polypeptide may comprise a stop codon (such as TAA, TAG, or TGA), positioned at, as a non-limiting example, at the 3' end of a nucleotide encoding an IL-15R α polypeptide.

[00372] In embodiments an IL-15 polypeptide and an IL-15R α polypeptide is linked by one or more linker. In embodiments, a linker is a peptide linker. In embodiments, a peptide linker is rigid or flexible. In embodiments, a linker is cleavable. In embodiments, a linker may promote stability or proper folding of a fusion polypeptide, may increase expression of a fusion polypeptide, may improve biological activity of a fusion polypeptide, may facilitate targeting of a fusion polypeptide, may alter the PK of a fusion polypeptide, or any combination thereof.

[00373] In embodiments a linker comprises about 2-40 amino acids, about 4-38 amino acids, about 6-34 amino acids, about 8-32 amino acids, about 10-30 amino acids, about 10 amino acids, about 11 amino acids, about 12 amino acids, about 12-28 amino acids, about 13 amino acids, about 14 amino acids, about 15 amino acids, about 16 amino acids, about 17 amino acids, about 18 amino acids, about 19 amino acids, about 20 amino acids, about 14-26 amino acids, about 12-24 amino acids, about 10-22 amino acids, about 10-20 amino acids, about 12-18 amino acids, about 14-16 amino acids, about 8-22 amino acids, about 6-24 amino acids, about 4-26 amino acids, or about 2-28 amino acids.

[00374] In embodiments one or more linker of an IL-15/IL-15R α fusion polypeptide independently comprises or consists of any of GSG, LE, SEQ ID NO: 266, 383, 385, 387, 389, 391, or 393, or 395-432 or a sequence having at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to any of SEQ ID NO: 266, 383, 385, 387, 389, 391, or 393, or 395-432. However, in embodiments, one or more linker of an IL-15/IL-15R α fusion polypeptide is not SEQ ID NO: 391 and/or SEQ ID NO: 395. In embodiments one or more linker of an IL-15/IL-15R α fusion polypeptide independently comprises or consists of any of GSG, LE, SEQ ID NO: 266, 383, 385, 387, 389, 393, or 396-432 or a sequence having at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to any of SEQ ID NO: 266, 383, 385, 387,

389, 393, or 396-432. In embodiments one or more linker of an IL-15/IL-15R α fusion polypeptide independently comprises or consists of any of SEQ ID NO: 383, 385, 387, or 389 or a sequence having at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to any of SEQ ID NO: 383, 385, 387, or 389.

[00375] In embodiments one or more linker of an IL-15/IL-15R α fusion polypeptide is independently encoded by one or more nucleic acid comprising or consisting of any of SEQ ID NO: 384, 386, 388, 390, or 392, by a sequence having at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identity to any of SEQ ID NO: 384, 386, 388, 390, or 392, by one or more nucleic acid encoding any linker comprising or consisting of GSG, LE, or one or more linker set forth in SEQ ID NO: 266 or 393-432, or by one or more nucleic acid encoding any linker having at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identity to any of SEQ ID NO: 266 or 393-432. However, in embodiments, one or more linker of an IL-15/IL-15R α fusion polypeptide is not encoded by SEQ ID NO: 392 and is not encoded by a nucleic acid encoding SEQ ID NO: 391 or 395.

[00376] In embodiments one or more linker of an IL-15/IL-15R α fusion polypeptide is independently encoded by one or more nucleic acid comprising or consisting of any of SEQ ID NO: 384, 386, 388, or 390, by a sequence having at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identity to any of SEQ ID NO: 384, 386, 388, or 390, by one or more nucleic acid encoding any linker comprising or consisting of GSG or one or more linker set forth in SEQ ID NO: 266, 383, 385, 387, 389, 393, or 396-432, or by one or more nucleic acid encoding any linker having at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identity to any of SEQ ID NO: 266, 383, 385, 387, 389, 393, or 396-432.

[00377] In embodiments one or more linker of an IL-15/IL-15R α fusion polypeptide is independently encoded by any of SEQ ID NO: 384, 386, 388, or 390 or by a sequence having at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%,

at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identity to any of SEQ ID NO: 384, 386, 388, or 390.

[00378] In embodiments a linker has a sequence comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the amino acid sequence of SEQ ID NO: 383. In embodiments a linker has a sequence comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the amino acid sequence of SEQ ID NO: 385. In embodiments a linker has a sequence comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the amino acid sequence of SEQ ID NO: 387. In embodiments a linker has a sequence comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the amino acid sequence of SEQ ID NO: 389. In embodiments, one or more function(s) of a linker, such as, but not limited to, one or more of flexibility, rigidity, cleavability, ability to promote stability or proper folding of a fusion polypeptide, ability to increase expression of a fusion polypeptide, ability improve biological activity of a fusion polypeptide, ability facilitate targeting of a fusion polypeptide, ability to alter the PK of a fusion polypeptide, or a combination thereof, of the linker, are preserved and/or enhanced in a mutated linker.

[00379] In embodiments a linker comprises (a) SEQ ID NO: 383 comprising one, two, three, four, or five amino acid substitutions; (b) SEQ ID NO: 385 comprising one, two, three, four, or five amino acid substitutions; (c) SEQ ID NO: 387 comprising one, two, three, four, or five amino acid substitutions; (d) SEQ ID NO: 389 comprising one, two, three, four, or five amino acid substitutions; or (e) SEQ ID NO: 391 comprising one, two, three, four, or five amino acid substitutions. In embodiments, amino acid substitutions may be conservative or non-conservative. In embodiments amino acid substitution(s) may be conservative amino acid substitution(s). In embodiments, one or more function(s) of a linker, such as, but not limited to, one or more of flexibility, rigidity, cleavability, ability to promote stability or proper folding of a fusion polypeptide, ability to increase expression of a fusion polypeptide, ability improve

biological activity of a fusion polypeptide, ability facilitate targeting of a fusion polypeptide, ability to alter the PK of a fusion polypeptide, or a combination thereof, of the linker, are preserved and/or enhanced in a mutated linker.

[00380] In embodiments a linker is encoded by a nucleic acid comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the nucleic acid of SEQ ID NO: 384. In embodiments a linker is encoded by a nucleic acid comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the nucleic acid of SEQ ID NO: 386. In embodiments a linker is encoded by a nucleic acid comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the nucleic acid of SEQ ID NO: 388. In embodiments a linker is encoded by a nucleic acid comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the nucleic acid of SEQ ID NO: 390. In embodiments, one or more function(s) of a linker, such as, but not limited to, one or more of flexibility, rigidity, cleavability, ability to promote stability or proper folding of a fusion polypeptide, ability to increase expression of a fusion polypeptide, ability improve biological activity of a fusion polypeptide, ability facilitate targeting of a fusion polypeptide, ability to alter the PK of a fusion polypeptide, or a combination thereof, of the linker, are preserved and/or enhanced in a mutated linker.

[00381] In embodiments a linker is encoded by a nucleic acid comprising (a) SEQ ID NO: 384 comprising one, two, three, four, or five nucleic acid substitutions; (b) SEQ ID NO: 386 comprising one, two, three, four, or five nucleic acid substitutions; (c) SEQ ID NO: 388 comprising one, two, three, four, or five nucleic acid substitutions; (d) SEQ ID NO: 390 comprising one, two, three, four, or five nucleic acid substitutions; or (e) SEQ ID NO: 392 comprising one, two, three, four, or five nucleic acid substitutions. In embodiments, one or more nucleic acid substitution in a codon may result in a codon encoding the same amino acid or may result in a codon encoding a different amino acid. In embodiments, one or more nucleic acid substitution in a codon may result in a codon encoding a conservative amino acid substitution. In embodiments, one or more nucleic acid substitution in a codon may result in a codon encoding

the same amino acid. In embodiments, one or more function(s) of a linker, such as, but not limited to, one or more of flexibility, rigidity, cleavability, ability to promote stability or proper folding of a fusion polypeptide, ability to increase expression of a fusion polypeptide, ability improve biological activity of a fusion polypeptide, ability facilitate targeting of a fusion polypeptide, ability to alter the PK of a fusion polypeptide, or a combination thereof, of the linker, are preserved and/or enhanced in a mutated linker.

[00382] In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker comprises SEQ ID NO: 317, 319, 321, 323, 325, 327, 329, 331, 333, or 335. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker is encoded by a nucleic acid comprising SEQ ID NO: 318, 320, 322, 324, 326, 328, 330, 332, 334, or 336. However, In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker does not comprise or consist of SEQ ID NO: 335 or sequences having about 95% or more sequence identity thereto. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker is not encoded by a nucleic acid comprising or consisting of SEQ ID NO: 336 or by sequences having about 80%, about 85%, about 90%, or about 95% or more sequence identity thereto. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker comprises SEQ ID NO: 317, 319, 321, 323, 325, 327, 329, 331, or 333. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker is encoded by a nucleic acid comprising SEQ ID NO: 318, 320, 322, 324, 326, 328, 330, 332, or 334. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker comprises SEQ ID NO: 317, 321, 325, 327, 329, 331, or 333. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker is encoded by a nucleic acid comprising SEQ ID NO: 318, 322, 326, 328, 330, 332, or 334.

[00383] In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker may comprise (a) SEQ ID NO: 317 comprising one, two, three, four, or five amino acid substitutions; (b) SEQ ID NO: 319 comprising one, two, three, four, or five amino acid substitutions; (c) SEQ ID NO: 321 comprising one, two, three, four, or five amino acid substitutions; (d) SEQ ID NO: 323 comprising one, two, three, four, or five amino acid substitutions; (e) SEQ ID NO: 325 comprising one, two, three, four, or five amino acid substitutions; (f) SEQ ID NO: 327 comprising one, two, three, four, or five amino acid substitutions; (g) SEQ ID NO: 329 comprising one, two, three, four, or five amino acid substitutions; (h) SEQ ID NO: 331 comprising one, two, three, four, or five amino acid substitutions; (i) SEQ ID NO: 333 comprising one, two, three, four, or five amino acid substitutions; or (j) SEQ ID NO: 335 comprising one, two, three, four, or five amino acid substitutions. However, In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker does not comprise or consist of SEQ ID NO: 335 or sequences having about 95% or more sequence identity thereto. In embodiments,

amino acid substitutions may be conservative or non-conservative. In embodiments amino acid substitution(s) may be conservative amino acid substitution(s). In embodiments, (i) function(s) of IL-15, such as, but not limited to, one or more signaling function(s) of IL-15, (ii) function(s) of IL-15R α , such as, but not limited to, the ability of IL-15R α be membrane-bound, and signaling function(s) of IL-15R α or (iii) both (i) and (ii), are preserved and/or enhanced in a mutated IL-15/IL-15R α fusion polypeptide.

[00384] In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker may comprise at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to SEQ ID NO: 317. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker may comprise at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to SEQ ID NO: 319. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker may comprise at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to SEQ ID NO: 321. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker may comprise at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to SEQ ID NO: 323. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker may comprise at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to SEQ ID NO: 325. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker may comprise at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to SEQ ID NO: 327. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker may comprise at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to SEQ ID NO: 329. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker may

comprise at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to SEQ ID NO: 331. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker may comprise at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to SEQ ID NO: 333. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker may comprise at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, or at least about 94% sequence identity to SEQ ID NO: 335. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker does not comprise or consist of SEQ ID NO: 335 or sequences having about 95% or more sequence identity thereto. In embodiments, (i) function(s) of IL-15, such as, but not limited to, one or more signaling function(s) of IL-15, (ii) function(s) of IL-15R α , such as, but not limited to, the ability of IL-15R α be membrane-bound, and signaling function(s) of IL-15R α or (iii) both (i) and (ii), are preserved and/or enhanced in an IL-15/IL-15R α fusion polypeptide encoded by a mutated nucleic acid sequence.

[00385] In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker may be encoded by a nucleic acid comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the nucleic acid of SEQ ID NO: 318. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker may be encoded by a nucleic acid comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the nucleic acid of SEQ ID NO: 320. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker may be encoded by a nucleic acid comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the nucleic acid of SEQ ID NO: 322. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker may be encoded by a nucleic acid comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to

the nucleic acid of SEQ ID NO: 324. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker may be encoded by a nucleic acid comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the nucleic acid of SEQ ID NO: 326. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker may be encoded by a nucleic acid comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the nucleic acid of SEQ ID NO: 328. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker may be encoded by a nucleic acid comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the nucleic acid of SEQ ID NO: 330. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker may be encoded by a nucleic acid comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the nucleic acid of SEQ ID NO: 332. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker may be encoded by a nucleic acid comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the nucleic acid of SEQ ID NO: 334. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker may be encoded by a nucleic acid comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, or at least about 94% sequence identity to the nucleic acid of SEQ ID NO: 336. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker is not encoded by a nucleic acid encoding a polypeptide having about 95% or more sequence identity to SEQ ID NO: 335. In embodiments, (i) function(s) of IL-15, such as, but not limited to, one or more signaling function(s) of IL-15, (ii) function(s) of IL-15R α , such as, but not limited to, the ability of IL-15R α be membrane-bound and one or more signaling function(s) of IL-15R α or (iii) both (i) and (ii), are preserved and/or enhanced in an IL-15/IL-15R α fusion polypeptide encoded by a mutated nucleic acid sequence.

[00386] In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker may be encoded by a nucleic acid comprising (a) SEQ ID NO: 318 comprising one, two, three, four, or

five nucleic acid substitutions; (b) SEQ ID NO: 320 comprising one, two, three, four, or five nucleic acid substitutions; (c) SEQ ID NO: 322 comprising one, two, three, four, or five nucleic acid substitutions; (d) SEQ ID NO: 324 comprising one, two, three, four, or five nucleic acid substitutions; (e) SEQ ID NO: 326 comprising one, two, three, four, or five nucleic acid substitutions; (f) SEQ ID NO: 328 comprising one, two, three, four, or five nucleic acid substitutions; (g) SEQ ID NO: 330 comprising one, two, three, four, or five nucleic acid substitutions; (h) SEQ ID NO: 332 comprising one, two, three, four, or five nucleic acid substitutions; or (i) SEQ ID NO: 334 comprising one, two, three, four, or five nucleic acid substitutions. In embodiments, one or more nucleic acid substitution in a codon may result in a codon encoding the same amino acid or may result in a codon encoding a different amino acid. In embodiments, one or more nucleic acid substitution in a codon may result in a codon encoding a conservative amino acid substitution. In embodiments, one or more nucleic acid substitution in a codon may result in a codon encoding the same amino acid. In embodiments, (i) function(s) of IL-15, such as, but not limited to, one or more signaling function(s) of IL-15, (ii) function(s) of IL-15R α , such as, but not limited to, the ability of IL-15R α be membrane-bound and one or more signaling function(s) of IL-15R α or (iii) both (i) and (ii), are preserved and/or enhanced in an IL-15/IL-15R α fusion polypeptide encoded by a mutated nucleic acid sequence.

[00387] In embodiments an IL-15/IL-15R α fusion polypeptide, optionally comprising one or more linker, comprises or consists of, e.g., SEQ ID NO: 307 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) directly or indirectly fused to an N terminus of SEQ ID NO: 309 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) with or without a linker therebetween; SEQ ID NO: 307 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) directly or indirectly fused to an N terminus of SEQ ID NO: 311 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) with or without a linker therebetween; SEQ ID NO: 307 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%,

at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) directly or indirectly fused to an N terminus of SEQ ID NO: 313 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) with or without a linker therebetween; or SEQ ID NO: 307 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) directly or indirectly fused to an N terminus of SEQ ID NO: 315 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) with or without a linker therebetween; or SEQ ID NO: 317, 319, 321, 323, 325, 327, 329, 331, 333, or 335 or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 317, 319, 321, 323, 325, 327, 329, 331, 333, or 335. However, In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker does not comprise or consist of (i) SEQ ID NO: 307 directly or indirectly fused to an N terminus of SEQ ID NO: 309 with a linker therebetween; (ii) SEQ ID NO: 335, (iii) sequences having about 95% or more sequence identity to SEQ ID NO: 307 directly or indirectly fused to an N terminus of SEQ ID NO: 309 with a linker therebetween; or (iv) sequences having about 95% or more sequence identity to SEQ ID NO: 335. In embodiments one or more linkers comprises or consists of a linker sequence set forth herein.

[00388] In embodiments an IL-15/IL-15R α fusion polypeptide, optionally comprising one or more linker, comprises or consists of, e.g., SEQ ID NO: 307 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) directly or indirectly fused to an N terminus of SEQ ID NO: 311 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) with or without a linker therebetween; SEQ ID NO: 307 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at

least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) directly or indirectly fused to an N terminus of SEQ ID NO: 313 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) with or without a linker therebetween; or SEQ ID NO: 307 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) directly or indirectly fused to an N terminus of SEQ ID NO: 315 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) with or without a linker therebetween; or SEQ ID NO: 317, 319, 321, 323, 325, 327, 329, 331, or 333 or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 317, 319, 321, 323, 325, 327, 329, 331, or 333. In embodiments one or more linkers comprises or consists of a linker sequence set forth herein.

[00389] In embodiments an IL-15/IL-15R α fusion polypeptide comprising one or more linker comprises or consists of, e.g., SEQ ID NO: 317, 321, 325, 327, 329, 331, or 333 or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 317, 321, 325, 327, 329, 331, or 333.

[00390] In embodiments an IL-15/IL-15R α fusion polypeptide, optionally comprising one or more linker, is encoded by a nucleic acid comprising or consisting of, e.g., SEQ ID NO: 308 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) directly or indirectly fused to the 5' end of SEQ ID NO: 310 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) with or without a nucleic acid encoding a linker therebetween; SEQ ID NO: 308 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%,

at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) directly or indirectly fused to the 5' end of SEQ ID NO: 312 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) with or without a nucleic acid encoding a linker therebetween; SEQ ID NO: 308 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) directly or indirectly fused to the 5' end of SEQ ID NO: 314 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) with or without a nucleic acid encoding a linker therebetween; or SEQ ID NO: 308 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) directly or indirectly fused to the 5' end of SEQ ID NO: 316 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) with or without a nucleic acid encoding a linker therebetween; or SEQ ID NO: 318, 320, 322, 324, 326, 328, 330, 332, 334, or 336 or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 318, 320, 322, 324, 326, 328, 330, 332, 334, or 336. However, In embodiments an IL-15/IL-15R α fusion polypeptide is not encoded by a nucleic acid comprising or consisting of (i) SEQ ID NO: 308 fused to the 5' end of SEQ ID NO: 310 with a linker therebetween; (ii) SEQ ID NO: 336, (iii) sequences having about 80%, about 85%, about 90%, or about 95% or more sequence identity to SEQ ID NO: 308 fused to the 5' end of SEQ ID NO: 310 with a linker therebetween; or (iv) sequences having about 80%, about 85%, about 90%, or about 95% or more sequence identity to SEQ ID NO: 336. In embodiments one or more linkers is encoded by one or more nucleic acid comprising or consisting of a nucleic acid encoding a linker set forth herein.

[00391] In embodiments an IL-15/IL-15R α fusion polypeptide, optionally comprising one or more linker, is encoded by a nucleic acid comprising or consisting of, e.g., SEQ ID NO: 308 (or

a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) directly or indirectly fused to the 5' end of SEQ ID NO: 312 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) with or without a nucleic acid encoding a linker therebetween; SEQ ID NO: 308 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) directly or indirectly fused to the 5' end of SEQ ID NO: 314 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) with or without a nucleic acid encoding a linker therebetween; or SEQ ID NO: 308 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) directly or indirectly fused to the 5' end of SEQ ID NO: 316 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) with or without a nucleic acid encoding a linker therebetween; or SEQ ID NO: 318, 320, 322, 324, 326, 328, 330, 332, or 334 or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 318, 320, 322, 324, 326, 328, 330, 332, or 334. In embodiments one or more linkers is encoded by one or more nucleic acid comprising or consisting of a nucleic acid encoding a linker set forth herein.

[00392] In embodiments an IL-15/IL-15R α fusion polypeptide is encoded by a nucleic acid comprising or consisting of, e.g., SEQ ID NO: 318, 322, 326, 328, 330, 332, or 334 or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 318, 322, 326, 328, 330, 332, or 334.

[00393] In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker (L) comprises or consists of any construct A-J as set forth in FIG. 69A. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker (L) comprises or consists of any construct A-I as set forth in FIG. 69A. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker comprises or consists of any construct A, C, or E-I as set forth in FIG. 69A. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker is encoded by one or more nucleic acid comprising or consisting of any construct A'-J' as set forth in FIG. 69B. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker is encoded by one or more nucleic acid comprising or consisting of any construct A'-I' as set forth in FIG. 69B. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker is encoded by one or more nucleic acid comprising or consisting of any construct A', C', or E'-I' as set forth in FIG. 69B. In embodiments, sequences comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identity to any of the sequences set forth in FIGs. 69A and 69B are also provided. In FIGs. 69A and 69B, the lines connecting the IL-15 to the linker and the linker to the IL-15R α may represent direct linkages, with no intervening sequences, or may represent intervening sequences, such as, but not limited to, a linker, an untranslated sequence (in the case of FIG. 69B), a translated sequence, a sequence comprising one or more restriction endonuclease sites (in the case of FIG. 69B), or a combination thereof.

[00394] In embodiments, a nucleic acid encoding an IL-15/IL-15R α fusion polypeptide may comprise a stop codon (such as TAA, TAG, or TGA), positioned at, as non-limiting examples, at the 3' end of a nucleotide encoding an IL-15R α polypeptide, such as where the encoded fusion polypeptide is in an orientation shown in FIG. 67A or FIG. 668A or at the 3' end of the IL-15 polypeptide, such as where the encoded fusion polypeptide is in an orientation shown in FIG. 67B or FIG. 668B.

[00395] In embodiments IL-15/IL-15R α fusion polypeptide and/or an IL-15R α /IL-15 fusion polypeptide may comprise one or more signal peptide. In embodiments a fusion polypeptide may comprise the entirety or a portion(s) of the short or the long signal peptide of IL-15 or the entirety or a portion(s) of the signal peptide of IL-15R α . In embodiments the entire signal peptide or part of the signal peptide of IL-15, IL-15R α , or both, may be mutated or deleted. In embodiments a fusion polypeptide may comprise one or more heterologous signal peptide, *i.e.*, the entirety or a portion of the signal peptide from a molecule other than IL-15 and IL-15R α . In embodiments, a heterologous signal peptide may be derived from IL-2, CD33, IgV κ , or IgE. In embodiments, a signal peptide may be a signal peptide derived from IgE. In embodiments a

signal peptide derived from IgE may comprise or consist of SEQ ID NO: 367. In embodiments a signal peptide derived from IgE may be encoded by a nucleic acid comprising or consisting of the sequence set forth in SEQ ID NO: 368.

[00396] In embodiments a signal peptide may be cleaved or otherwise removed from an IL-15/IL-15R α fusion polypeptide.

[00397] In embodiments, a signal peptide may increase or facilitate transcription, translation, translocation, or a combination thereof, of a fusion polypeptide, as compared to a native IL-15R α signal peptide, a native IL-15 signal peptide, or both. In embodiments, the signal peptide may be directly or indirectly fused to the N-terminus or to the C-terminus of an IL-15/IL-15R α fusion polypeptide.

[00398] In embodiments a signal peptide has a sequence comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the amino acid sequence of SEQ ID NO: 367. In embodiments, function(s) of a signal peptide, such as, but not limited to, one or more signaling function(s) of the signal peptide, are preserved and/or enhanced in a mutated signal peptide.

[00399] In embodiments a signal peptide may comprise SEQ ID NO: 367 comprising one, two, three, four, or five amino acid substitutions. In embodiments, function(s) of a signal peptide, such as, but not limited to, one or more signaling function(s) of the signal peptide, are preserved and/or enhanced in a mutated signal peptide.

[00400] In embodiments a signal peptide may be encoded by a nucleic acid comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the nucleic acid of SEQ ID NO: 368. In embodiments, function(s) of a signal peptide, such as, but not limited to, one or more signaling function(s) of the signal peptide, are preserved and/or enhanced in a signal peptide that is encoded by a mutated nucleic acid sequence.

[00401] In embodiments a signal peptide may be encoded by a nucleic acid comprising SEQ ID NO: 368 comprising one, two, three, four, or five nucleic acid substitutions. In embodiments, one or more nucleic acid substitution in a codon may result in a codon encoding the same amino acid or may result in a codon encoding a different amino acid. In embodiments, one or more nucleic acid substitution in a codon may result in a codon encoding a conservative amino acid substitution. In embodiments, one or more nucleic acid substitution in a codon may result in a codon encoding the same amino acid. In embodiments, function(s) of a signal peptide, such as,

but not limited to, one or more signaling function(s) of the signal peptide, are preserved and/or enhanced in a signal peptide that is encoded by a mutated nucleic acid sequence.

[00402] In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker and a signal peptide derived from IgE may comprise at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to SEQ ID NO: 337. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker and a signal peptide derived from IgE may comprise at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to SEQ ID NO: 339. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker and a signal peptide derived from IgE may comprise at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to SEQ ID NO: 341. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker and a signal peptide derived from IgE may comprise at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to SEQ ID NO: 343. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker and a signal peptide derived from IgE may comprise at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to SEQ ID NO: 345. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker and a signal peptide derived from IgE may comprise at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to SEQ ID NO: 347. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker and a signal peptide derived from IgE may comprise at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to SEQ ID NO: 349. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker and a signal peptide derived from IgE may comprise at least about 80%, at least about 85%, at least about 90%, at

least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to SEQ ID NO: 351. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker and a signal peptide derived from IgE may comprise at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to SEQ ID NO: 353. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker and a signal peptide derived from IgE may comprise at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to SEQ ID NO: 355. However, In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker and a signal peptide derived from IgE does not comprise or consist of SEQ ID NO: 355 or sequences having about 95% or more sequence identity thereto. In embodiments, (i) function(s) of IL-15, such as, but not limited to, one or more signaling function(s) of IL-15, (ii) function(s) of IL-15R α , such as, but not limited to, the ability of IL-15R α be membrane-bound and one or more signaling function(s) of IL-15R α (iii) function(s) of a signal peptide derived from IgE, such as, but not limited to, one or more signaling function(s) of the signal peptide, or (iv) all of (i), (ii), and (iii), are preserved and/or enhanced in a mutated IL-15/IL-15R α fusion polypeptide comprising a signal peptide derived from IgE.

[00403] In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker and a signal peptide derived from IgE may comprise (a) SEQ ID NO: 337 comprising one, two, three, four, or five amino acid substitutions; (b) SEQ ID NO: 339 comprising one, two, three, four, or five amino acid substitutions; (c) SEQ ID NO: 341 comprising one, two, three, four, or five amino acid substitutions; (d) SEQ ID NO: 343 comprising one, two, three, four, or five amino acid substitutions; (e) SEQ ID NO: 345 comprising one, two, three, four, or five amino acid substitutions; (f) SEQ ID NO: 347 comprising one, two, three, four, or five amino acid substitutions; (g) SEQ ID NO: 349 comprising one, two, three, four, or five amino acid substitutions; (h) SEQ ID NO: 351 comprising one, two, three, four, or five amino acid substitutions; (i) SEQ ID NO: 353 comprising one, two, three, four, or five amino acid substitutions; or (j) SEQ ID NO: 355 comprising one, two, three, four, or five amino acid substitutions. However, In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker and a signal peptide derived from IgE does not comprise or consist of SEQ ID NO: 355 or sequences having about 95% or more sequence identity thereto. In embodiments, amino acid substitutions may be conservative or non-conservative. In embodiments amino acid

substitution(s) may be conservative amino acid substitution(s). In embodiments, (i) function(s) of IL-15, such as, but not limited to, one or more signaling function(s) of IL-15, (ii) function(s) of IL-15R α , such as, but not limited to, the ability of IL-15R α be membrane-bound and one or more signaling function(s) of IL-15R α , (iii) function(s) of a signal peptide derived from IgE, such as, but not limited to, one or more signaling function(s) of the signal peptide, or (iv) all of (i), (ii), and (iii), are preserved and/or enhanced in a mutated IL-15/IL-15R α fusion polypeptide comprising a signal peptide derived from IgE.

[00404] In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker and a signal peptide derived from IgE may be encoded by a nucleic acid comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the nucleic acid of SEQ ID NO: 338. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker and a signal peptide derived from IgE may be encoded by a nucleic acid comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the nucleic acid of SEQ ID NO: 340. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker and a signal peptide derived from IgE may be encoded by a nucleic acid comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the nucleic acid of SEQ ID NO: 342. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker and a signal peptide derived from IgE may be encoded by a nucleic acid comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the nucleic acid of SEQ ID NO: 344. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker and a signal peptide derived from IgE may be encoded by a nucleic acid comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the nucleic acid of SEQ ID NO: 346. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker and a signal peptide derived from IgE may be encoded by a nucleic acid comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least

about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the nucleic acid of SEQ ID NO: 348. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker and a signal peptide derived from IgE may be encoded by a nucleic acid comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the nucleic acid of SEQ ID NO: 350. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker and a signal peptide derived from IgE may be encoded by a nucleic acid comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the nucleic acid of SEQ ID NO: 352. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker and a signal peptide derived from IgE may be encoded by a nucleic acid comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the nucleic acid of SEQ ID NO: 354. In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker and a signal peptide derived from IgE may be encoded by a nucleic acid comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the nucleic acid of SEQ ID NO: 356. However, In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker and a signal peptide derived from IgE is not encoded by SEQ ID NO: 356 or sequences having about 80%, about 85%, about 90%, or about 95% or more sequence identity thereto. In embodiments, (i) function(s) of IL-15, such as, but not limited to, one or more signaling function(s) of IL-15, (ii) function(s) of IL-15R α , such as, but not limited to, the ability of IL-15R α be membrane-bound and one or more signaling function(s) of IL-15R α , (iii) function(s) of a signal peptide derived from IgE, such as, but not limited to, one or more signaling function(s) of the signal peptide, or (iv) all of (i), (ii), and (iii), are preserved and/or enhanced in an IL-15/IL-15R α fusion polypeptide comprising a signal peptide derived from IgE, that is encoded by a mutated nucleic acid sequence.

[00405] In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker and a signal peptide derived from IgE may be encoded by a nucleic acid comprising (a) SEQ ID NO: 338 comprising one, two, three, four, or five nucleic acid substitutions; (b) SEQ ID NO: 340

comprising one, two, three, four, or five nucleic acid substitutions; (c) SEQ ID NO: 342 comprising one, two, three, four, or five nucleic acid substitutions; (d) SEQ ID NO: 344 comprising one, two, three, four, or five nucleic acid substitutions; (e) SEQ ID NO: 346 comprising one, two, three, four, or five nucleic acid substitutions; (f) SEQ ID NO: 348 comprising one, two, three, four, or five nucleic acid substitutions; (g) SEQ ID NO: 350 comprising one, two, three, four, or five nucleic acid substitutions; (h) SEQ ID NO: 352 comprising one, two, three, four, or five nucleic acid substitutions; (i) SEQ ID NO: 354 comprising one, two, three, four, or five nucleic acid substitutions; or (j) SEQ ID NO: 356 comprising one, two, three, four, or five nucleic acid substitutions. However, In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker and a signal peptide derived from IgE is not encoded by SEQ ID NO: 356 or sequences having about 80%, about 85%, about 90%, or about 95% or more sequence identity thereto. In embodiments, one or more nucleic acid substitution in a codon may result in a codon encoding the same amino acid or may result in a codon encoding a different amino acid. In embodiments, one or more nucleic acid substitution in a codon may result in a codon encoding a conservative amino acid substitution. In embodiments, (i) function(s) of IL-15, such as, but not limited to, one or more signaling function(s) of IL-15, (ii) function(s) of IL-15R α , such as, but not limited to, the ability of IL-15R α be membrane-bound and one or more signaling function(s) of IL-15R α , (iii) function(s) of a signal peptide derived from IgE, such as, but not limited to, one or more signaling function(s) of the signal peptide, or (iv) all of (i), (ii), and (iii), are preserved and/or enhanced in an IL-15/IL-15R α fusion polypeptide comprising a signal peptide derived from IgE, that is encoded by a mutated nucleic acid sequence.

[00406] In embodiments an IL-15/IL-15R α fusion polypeptide comprising a signal peptide derived from IgE, and optionally comprising one or more linker, comprises or consists of, e.g., SEQ ID NO: 367 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) directly or indirectly fused to the N terminus of SEQ ID NO: 307 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) directly or indirectly fused to the N terminus of SEQ ID NO: 309 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) with or without a linker therebetween;

- 88 -

about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 337, 339, 341, 343, 345, 347, 349, 351, 353, or 355. However, In embodiments an IL-15/IL-15R α fusion polypeptide comprising a signal peptide derived from IgE, and optionally comprising one or more linker does not comprise or consist of (i) SEQ ID NO: 307 directly or indirectly fused to the N terminus of SEQ ID NO: 309 with a linker therebetween; (ii) SEQ ID NO: 335 or SEQ ID NO: 355; (iii) sequences having about 95% or more sequence identity to SEQ ID NO: 307 directly or indirectly fused to the N terminus of SEQ ID NO: 309 with a linker therebetween; or (iv) sequences having about 95% or more sequence identity to SEQ ID NO: 335 or SEQ ID NO: 355. In embodiments one or more linkers comprises or consists of a linker sequence set forth herein.

[00407] In embodiments an IL-15/IL-15R α fusion polypeptide comprising a signal peptide derived from IgE, and optionally comprising one or more linker, comprises or consists of, e.g., SEQ ID NO: 367 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) directly or indirectly fused to the N terminus of SEQ ID NO: 307 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) directly or indirectly fused to the N terminus of SEQ ID NO: 311 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) with or without a linker therebetween; SEQ ID NO: 367 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) directly or indirectly fused to the N terminus of SEQ ID NO: 307 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) directly or indirectly fused to the N terminus of SEQ ID NO: 313 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) with or without a linker therebetween; or SEQ ID NO: 367 (or a sequence at least about 80%, at least about 85%, at least about 90%, at

least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) directly or indirectly fused to the N terminus of SEQ ID NO: 307 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) directly or indirectly fused to the N terminus of SEQ ID NO: 315 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) with or without a linker therebetween; or SEQ ID NO: 337, 339, 341, 343, 345, 347, 349, 351, or 353 or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 337, 339, 341, 343, 345, 347, 349, 351, or 353. In embodiments one or more linkers comprises or consists of a linker sequence set forth herein.

[00408] In embodiments an IL-15/IL-15R α fusion polypeptide comprising a signal peptide derived from IgE, and comprising a linker, comprises or consists of, e.g., SEQ ID NO: 337, 341, 345, 347, 349, 351, or 353 or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 337, 341, 345, 347, 349, 351, or 353.

[00409] In embodiments an IL-15/IL-15R α fusion polypeptide comprising a signal peptide derived from IgE, and optionally comprising one or more linker, is encoded by a nucleic acid comprising or consisting of, e.g., SEQ ID NO: 368 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) directly or indirectly fused to the 5' end of SEQ ID NO: 308 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) directly or indirectly fused to the 5' end of SEQ ID NO: 310 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) with or without a

nucleic acid encoding a linker therebetween; SEQ ID NO: 368 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) directly or indirectly fused to the 5' end of SEQ ID NO: 308 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) directly or indirectly fused to the 5' end of SEQ ID NO: 312 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) with or without a nucleic acid encoding a linker therebetween; SEQ ID NO: 368 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) directly or indirectly fused to the 5' end of SEQ ID NO: 308 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) directly or indirectly fused to the 5' end of SEQ ID NO: 314 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) with or without a nucleic acid encoding a linker therebetween; or SEQ ID NO: 368 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) directly or indirectly fused to the 5' end of SEQ ID NO: 308 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) directly or indirectly fused to the 5' end of SEQ ID NO: 316 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto); or SEQ ID NO: 338, 340, 342, 344, 346, 348, 350, 352, 354, or 356, or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least

about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 338, 340, 342, 344, 346, 348, 350, 352, 354, or 356.

[00410] However, In embodiments an IL-15/IL-15R α fusion polypeptide comprising a linker and a signal peptide derived from IgE is not encoded by a nucleic acid comprising or consisting of (i) SEQ ID NO: 356 or by sequences having about 80%, about 85%, about 90%, or about 95% or more sequence identity thereto or (ii) SEQ ID NO: 368 directly or indirectly fused to the 5' end of SEQ ID NO: 308 directly or indirectly fused to the 5' end of SEQ ID NO: 310 or by sequences having about 80%, about 85%, about 90%, or about 95% or more sequence identity thereto. In embodiments one or more linkers is encoded by one or more nucleic acid comprising or consisting of a nucleic acid encoding a linker set forth herein.

[00411] In embodiments an IL-15/IL-15R α fusion polypeptide comprising a signal peptide derived from IgE, and optionally comprising one or more linker, is encoded by a nucleic acid comprising or consisting of, e.g., SEQ ID NO: 368 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) directly or indirectly fused to the 5' end of SEQ ID NO: 308 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) directly or indirectly fused to the 5' end of SEQ ID NO: 312 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) with or without a nucleic acid encoding a linker therebetween; SEQ ID NO: 368 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) directly or indirectly fused to the 5' end of SEQ ID NO: 308 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) directly or indirectly fused to the 5' end of SEQ ID NO: 314 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) with or

without a nucleic acid encoding a linker therebetween; or SEQ ID NO: 368 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) directly or indirectly fused to the 5' end of SEQ ID NO: 308 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto) directly or indirectly fused to the 5' end of SEQ ID NO: 316 (or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto); or SEQ ID NO: 338, 340, 342, 344, 346, 348, 350, 352, or 354 or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 338, 340, 342, 344, 346, 348, 350, 352, or 354. In embodiments one or more linkers is encoded by one or more nucleic acid comprising or consisting of a nucleic acid encoding a linker set forth herein.

[00412] In embodiments an IL-15/IL-15R α fusion polypeptide comprising a signal peptide derived from IgE, and comprising one or more linker is encoded by a nucleic acid comprising or consisting of, e.g., SEQ ID NO: 338, 342, 346, 348, 350, 352, or 354 or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 338, 342, 346, 348, 350, 352, or 354.

[00413] In embodiments a vector may further comprise a post-transcriptional regulatory element (PRE) sequence. In embodiments the post-transcriptional regulatory element (PRE) sequence may be selected from a Woodchuck hepatitis virus PRE (WPRE) (such as, but not limited to wild type WPRE, such as but not limited to SEQ ID NO: 264, or a mutated WPRE, such as but not limited to WPREmut1 (SEQ ID NO: 256) or WPREmut2 (SEQ ID NO: 257)) or a hepatitis B virus (HBV) PRE (HPRE) (SEQ ID NO: 437), variant(s) thereof, or any combination thereof.

[00414] In embodiments (i) an IL-15/IL-15R α fusion polypeptide comprising a linker and a signal peptide derived from IgE (ii) followed by WPREmut2 may be encoded by a nucleic acid comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at

least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the nucleic acid of SEQ ID NO: 357. In embodiments (i) an IL-15/IL-15R α fusion polypeptide comprising a linker and a signal peptide derived from IgE (ii) followed by WPREmut2 may be encoded by a nucleic acid comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the nucleic acid of SEQ ID NO: 358. In embodiments (i) an IL-15/IL-15R α fusion polypeptide comprising a linker and a signal peptide derived from IgE (ii) followed by WPREmut2 may be encoded by a nucleic acid comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the nucleic acid of SEQ ID NO: 359. In embodiments (i) an IL-15/IL-15R α fusion polypeptide comprising a linker and a signal peptide derived from IgE (ii) followed by WPREmut2 may be encoded by a nucleic acid comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the nucleic acid of SEQ ID NO: 360. In embodiments (i) an IL-15/IL-15R α fusion polypeptide comprising a linker and a signal peptide derived from IgE (ii) followed by WPREmut2 may be encoded by a nucleic acid comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the nucleic acid of SEQ ID NO: 361. In embodiments (i) an IL-15/IL-15R α fusion polypeptide comprising a linker and a signal peptide derived from IgE (ii) followed by WPREmut2 may be encoded by a nucleic acid comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the nucleic acid of SEQ ID NO: 362. In embodiments (i) an IL-15/IL-15R α fusion polypeptide comprising a linker and a signal peptide derived from IgE (ii) followed by WPREmut2 may be encoded by a nucleic acid comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the nucleic acid of SEQ ID NO: 363. In embodiments (i) an IL-15/IL-15R α fusion polypeptide comprising a

linker and a signal peptide derived from IgE (ii) followed by WPREmut2 may be encoded by a nucleic acid comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the nucleic acid of SEQ ID NO: 364. In embodiments (i) an IL-15/IL-15R α fusion polypeptide comprising a linker and a signal peptide derived from IgE (ii) followed by WPREmut2 may be encoded by a nucleic acid comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the nucleic acid of SEQ ID NO: 365. In embodiments (i) an IL-15/IL-15R α fusion polypeptide comprising a linker and a signal peptide derived from IgE (ii) followed by WPRE may be encoded by a nucleic acid comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the nucleic acid of SEQ ID NO: 366. However, In embodiments (i) an IL-15/IL-15R α fusion polypeptide comprising a linker and a signal peptide derived from IgE (ii) followed by a mutant or wild type WPRE is not encoded by SEQ ID NO: 366 or sequences having about 80%, about 85%, about 90%, or about 95% or more sequence identity thereto. In embodiments, (i) function(s) of IL-15, such as, but not limited to, one or more signaling function(s) of IL-15, (ii) function(s) of IL-15R α , such as, but not limited to, the ability of IL-15R α be membrane-bound and signaling function(s) of IL-15R α , (iii) function(s) of a signal peptide derived from IgE, such as, but not limited to, one or more signaling function(s) of the signal peptide, (iv) post-transcriptional regulatory function(s) of wild type or mutant WPRE, or (v) all of (i), (ii), (iii), and (iv) are preserved and/or enhanced in an IL-15/IL-15R α fusion polypeptide comprising a signal peptide derived from IgE that is encoded by a mutated nucleic acid sequence.

[00415] In embodiments (i) an IL-15/IL-15R α fusion polypeptide comprising a linker and a signal peptide derived from IgE (ii) followed by WPREmut2 or wild type WPRE (wt where indicated) may be encoded by a nucleic acid comprising (a) SEQ ID NO: 357 comprising one, two, three, four, or five nucleic acid substitutions; (b) SEQ ID NO: 358 comprising one, two, three, four, or five nucleic acid substitutions; (c) SEQ ID NO: 359 comprising one, two, three, four, or five nucleic acid substitutions; (d) SEQ ID NO: 360 comprising one, two, three, four, or five nucleic acid substitutions; (e) SEQ ID NO: 361 comprising one, two, three, four, or five nucleic acid substitutions; (f) SEQ ID NO: 362 comprising one, two, three, four, or five nucleic acid substitutions; (g) SEQ ID NO: 363 comprising one, two, three, four, or five nucleic acid

substitutions; (h) SEQ ID NO: 364 comprising one, two, three, four, or five nucleic acid substitutions; (i) SEQ ID NO: 365 comprising one, two, three, four, or five nucleic acid substitutions; or (j) SEQ ID NO: 366 (wt WPRE) comprising one, two, three, four, or five nucleic acid substitutions. However, In embodiments (i) an IL-15/IL-15R α fusion polypeptide comprising a linker and a signal peptide derived from IgE (ii) followed by a wild type or mutant WPRE is not encoded by SEQ ID NO: 366 or sequences having about 80%, about 85%, about 90%, or about 95% or more sequence identity thereto. In embodiments, one or more nucleic acid substitution in a codon may result in a codon encoding the same amino acid or may result in a codon encoding a different amino acid. In embodiments, one or more nucleic acid substitution in a codon may result in a codon encoding a conservative amino acid substitution. In embodiments, one or more nucleic acid substitution in a codon may result in a codon encoding the same amino acid. In embodiments, (i) function(s) of IL-15, such as, but not limited to, one or more signaling function(s) of IL-15, (ii) function(s) of IL-15R α , such as, but not limited to, the ability of IL-15R α be membrane-bound and signaling function(s) of IL-15R α , (iii) function(s) of a signal peptide derived from IgE, such as, but not limited to, one or more signaling function(s) of the signal peptide, (iv) post-transcriptional regulatory function(s) of mutant or wild type WPRE, or (v) all of (i), (ii), (iii), and (iv) are preserved and/or enhanced in an IL-15/IL-15R α fusion polypeptide comprising a signal peptide derived from IgE that is encoded by a mutated nucleic acid sequence.

[00416] In embodiments nucleic acid sequences encoding a mbIL-15 polypeptide operatively coupled to a promoter are provided. In embodiments nucleic acid sequences encoding a mbIL-15 polypeptide operatively coupled to a post-transcriptional regulatory element are provided. In embodiments the promoter is an MSCV promoter and/or the post-transcriptional regulatory element is a WPRE, optionally a mutated WPRE, optionally WPREmut2. In embodiments the promoter is MSCV promoter. In embodiments the WPRE is WPREmut2.

[00417] In embodiments one or more vectors comprising one or more nucleic acids encoding SEQ ID NO: 305, 306, 307, 309, 311, 313, 315, 317, 319, 321, 323, 325, 327, 329, 331, 333, 335, 337, 339, 341, 343, 345, 347, 349, 351, 353, 355, or combinations thereof are provided. In embodiments one or more vectors comprising one or more nucleic acids encoding SEQ ID NO: 307, 311, 313, 315, 317, 319, 321, 323, 325, 327, 329, 331, 333, 337, 339, 341, 343, 345, 347, 349, 351, 353, or combinations thereof are provided. In embodiments one or more vectors comprising one or more nucleic acids encoding SEQ ID NO: 311, 313, 315, 317, 319, 321, 323, 325, 327, 329, 331, 333, 337, 339, 341, 343, 345, 347, 349, 351, 353, or combinations thereof are provided. In embodiments one or more vectors comprising one or more nucleic acids encoding SEQ ID NO: 311, 313, 315, 317, 321, 325, 327, 329, 331, 333, 337, 341, 345, 347,

349, 351, 353, or combinations thereof are provided. Such vectors may also comprise one or more nucleic acids encoding one or more TCR α , one or more TCR β , one or more CD8 α , one or more CD8 β , or combinations thereof. Each of TCR α , TCR β , CD8 α , and CD8 β may independently be modified or unmodified.

[00418] In embodiments one or more vectors comprising SEQ ID NO: 308, 310, 312, 314, 316, 318, 320, 322, 324, 326, 328, 330, 332, 334, 336, 338, 340, 342, 344, 346, 348, 350, 352, 354, 356-366, or combinations thereof are provided. In embodiments one or more vectors comprising SEQ ID NO: 308, 312, 314, 316, 318, 320, 322, 324, 326, 328, 330, 332, 334, 338, 340, 342, 344, 346, 348, 350, 352, 354, 357-365 or combinations thereof are provided. In embodiments one or more vectors comprising SEQ ID NO: 312, 314, 316, 318, 320, 322, 324, 326, 328, 330, 332, 334, 338, 340, 342, 344, 346, 348, 350, 352, 354, 357-365 or combinations thereof are provided. In embodiments one or more vectors comprising SEQ ID NO: 312, 314, 316, 318, 322, 326, 328, 330, 332, 334, 338, 342, 346, 348, 350, 352, 354, 357, 359, 361-365 or combinations thereof are provided. Such vectors may also comprise one or more nucleic acids encoding one or more TCR α , one or more TCR β , one or more CD8 α , one or more CD8 β , or combinations thereof. Each of TCR α , TCR β , CD8 α , and CD8 β may independently be modified or unmodified.

[00419] In embodiments one or more cells comprising one or more nucleic acids (such as in one or more vectors) encoding SEQ ID NO: 305, 306, 307, 309, 311, 313, 315, 317, 319, 321, 323, 325, 327, 329, 331, 333, 335, 337, 339, 341, 343, 345, 347, 349, 351, 353, 355, or combinations thereof are provided. In embodiments one or more cells comprising one or more nucleic acids (such as in one or more vectors) encoding SEQ ID NO: 311, 313, 315, 317, 319, 321, 323, 325, 327, 329, 331, 333, 337, 339, 341, 343, 345, 347, 349, 351, 353, or combinations thereof are provided. In embodiments one or more cells comprising one or more nucleic acids (such as in one or more vectors) encoding SEQ ID NO: 311, 313, 315, 317, 321, 325, 327, 329, 331, 333, 337, 341, 345, 347, 349, 351, 353, or combinations thereof are provided. Such cells may also comprise one or more nucleic acids (such as in one or more vectors) encoding one or more TCR α , one or more TCR β , one or more CD8 α , one or more CD8 β , or combinations thereof. Each of TCR α , TCR β , CD8 α , and CD8 β may independently be modified or unmodified.

[00420] In embodiments one or more cells transduced to express SEQ ID NO: 305, 306, 307, 309, 311, 313, 315, 317, 319, 321, 323, 325, 327, 329, 331, 333, 335, 337, 339, 341, 343, 345, 347, 349, 351, 353, 355, or combinations thereof are provided. In embodiments one or more cells transduced to express SEQ ID NO: 311, 313, 315, 317, 319, 321, 323, 325, 327, 329, 331, 333, 337, 339, 341, 343, 345, 347, 349, 351, 353, or combinations thereof are provided. In embodiments one or more cells transduced to express SEQ ID NO: 311, 313, 315, 317, 321, 325,

327, 329, 331, 333, 337, 341, 345, 347, 349, 351, 353, or combinations thereof are provided. Such cells may also be transduced to express one or more TCR α , one or more TCR β , one or more CD8 α , one or more CD8 β , or combinations thereof. Each of TCR α , TCR β , CD8 α , and CD8 β may independently be modified or unmodified.

[00421] In embodiments one or more cells comprising one or more nucleic acids (such as in one or more vectors) comprising SEQ ID NO: 308, 310, 312, 314, 316, 318, 320, 322, 324, 326, 328, 330, 332, 334, 336, 338, 340, 342, 344, 346, 348, 350, 352, 354, 356-366, or combinations thereof are provided. In embodiments one or more cells comprising one or more nucleic acids (such as in one or more vectors) SEQ ID NO: 312, 314, 316, 318, 320, 322, 324, 326, 328, 330, 332, 334, 338, 340, 342, 344, 346, 348, 350, 352, 354, 357-365 or combinations thereof are provided. In embodiments one or more cells comprising one or more nucleic acids (such as in one or more vectors) SEQ ID NO: 312, 314, 316, 318, 322, 326, 328, 330, 332, 334, 338, 342, 346, 348, 350, 352, 354, 357, 359, 361-365 or combinations thereof are provided. Such cells may also comprise one or more nucleic acids (such as in one or more vectors) encoding one or more TCR α , one or more TCR β , one or more CD8 α , one or more CD8 β , or combinations thereof. Each of TCR α , TCR β , CD8 α , and CD8 β may independently be modified or unmodified.

[00422] In embodiments nucleic acids do not encode, vectors do not encode, and/or cells do not comprise and/or are not transduced to express SEQ ID NO: 335 or 355 or any sequence having about 95% or more sequence identity to SEQ ID NO: 335 or 355. In embodiments nucleic acids, vectors, and/or cells do not comprise SEQ ID NO: 336, 356, or 366 or any sequence having about 80%, about 85%, about 90%, or about 95% or more sequence identity to SEQ ID NO: 336, 356, or 366.

[00423] In embodiments cells described herein may comprise a membrane-bound IL-15 and a CD8 polypeptide as described herein. In embodiments cells described herein may comprise an IL-15/IL-15R α fusion polypeptide and a CD8 polypeptide as described herein. In embodiments, cells described herein may comprise an IL-15/IL-15R α fusion polypeptide, a CD8 polypeptide, a cell receptor (TCR) comprising an α chain and a β chain, a TCR comprising an γ chain and a δ chain, a chimeric antigen receptor (CAR), or any combination thereof. In embodiments a cell may comprise an $\alpha\beta$ T cell, an $\gamma\delta$ T cell, a natural killer cell, a natural killer T cell, a CD4⁺ cell, a CD8⁺ cell, a CD4⁺/CD8⁺ cell, or combination thereof.

[00424] In embodiments expression of membrane-bound IL-15 may improve immune cell, such as but not limited to, T cell and/or natural killer cell, persistence, functionality, growth, viability, expansion, or any combination thereof, as compared to cells not expressing membrane-bound IL-15. In embodiments expression of membrane-bound IL-15 may improve immune cell, such as but not limited to, T cell and/or natural killer cell, persistence, functionality, growth,

viability, expansion, or any combination thereof, in a tumor microenvironment, as compared to cells not expressing membrane-bound IL-15. In embodiments expression of membrane-bound IL-15 may increase efficacy of immune cells, such as, but not limited to, T cells and/or natural killer cells, in killing tumor cells, as compared to cells not expressing membrane-bound IL-15. In embodiments expression of membrane-bound IL-15 may increase ability of immune cells, such as, but not limited to, T cells and/or natural killer cells, to survive in a tumor microenvironment, to persist in killing tumor cells, or any combination thereof, as compared to cells not expressing membrane-bound IL-15. In embodiments expression of membrane-bound IL-15 may increase ability of immune cells, such as, but not limited to, T cells and/or natural killer cells, to maintain a naïve phenotype.

[00425] Persistence may be assessed, as a non-limiting example, by the length of time cells are detectable in an individual (e.g., patient) after infusion. As non-limiting examples, persistence may be measured at days, weeks, months, or years after infusion, as non-limiting examples, at about 1 week, about 2 weeks, about 4 weeks, about 1 month, about 2 months, about 3 months, about 6 months, about 9 months, about 12 months, about 18 months, about 24 months, and/or about 30 months after infusion. Persistence may be assessed, as non-limiting examples, by PCR of peripheral blood sample(s), by flow cytometry of peripheral blood samples(s), and/or by analysis of tumor biopsy sample(s). Persistence of cells expressing membrane-bound IL-15 may be compared, as non-limiting examples, to typical persistence of infused ACT cells or persistence of similar cells not expressing membrane-bound IL-15.

[00426] Continued ability to kill tumor cells may be measured, as non-limiting examples, via (i) serial killing assays using an IncuCyte (wherein ability to kill/impair tumor growth as measured by fold growth during repeated tumor stimulations over a duration of time is assessed), and/or (ii) via cytokine/effector molecule production (IFN γ via ELISAs and other pro-inflammatory cytokines via Luminex (cytokines measured may include, as non-limiting examples, IFN γ , TNF α , Granzyme B, perforin, IL-2, IL-6, MIP-1 β , MIP-1 α , GM-CSF, RANTES, IL-18, IL-4, IL-10, and IP10)). Continued ability of cells expressing membrane-bound IL-15 to kill tumor cells may be compared, as non-limiting examples, to continued ability of similar cells not expressing membrane-bound IL-15 to kill tumor cells or continued ability of other control cells to kill tumor cells.

[00427] Naivety of phenotype may be assessed, as a non-limiting example, via Tmem panel assay via flow cytometry. Typically, flow cytometer gating is off of CD8+TCR+ cells. Typically, a more naïve phenotype may be indicated by higher frequencies of the T memory subsets Tnaïve/scm (CD45RA+CCR7+), and Tcm (CD45RA-CCR7+) and an increase or

retention of the CD39-CD69- and CD27+CD28+ populations. Low CD57 expression may also be desirable.

[00428] When assessing the persistence, functionality, growth, viability, expansion, tumor killing efficacy, naivety, or other characteristics of cells expressing dnTGFR β R2, cells such as non-transduced cells, cells transduced with TCR only, cells transduced with CD8 and TCR, or a combination thereof, may serve as control cells, as non-limiting examples.

[00429] In embodiments membrane-bound IL-15 may act in a *cis* manner (e.g., affecting cells in which it is expressed), in a *trans* manner (e.g., affecting cells in which it is not expressed), or any combination thereof. In embodiments in which membrane-bound IL-15 acts in *trans*, cells adjacent to or near (e.g., within the tumor microenvironment) cells expressing membrane-bound IL-15 may exhibit any or combination of improvements the same or similar to those described for cells expressing membrane-bound IL-15, as compared to cells not adjacent to or near cells expressing membrane-bound IL-15.

Modified CD8 Polypeptides

[00430] CD8 polypeptides described herein may comprise the general structure of a N-terminal signal peptide (optional), CD8 α immunoglobulin (Ig)-like domain, CD8 β stalk region (domain), CD8 α transmembrane domain, and a CD8 α cytoplasmic domain. The modified CD8 polypeptides described herein shown an unexpected improvement in functionality of T cells co-transduced with a vector expressing a TCR and CD8 polypeptide.

[00431] CD8 polypeptides described herein may comprise the general structure of a N-terminal signal peptide (optional), CD8 α immunoglobulin (Ig)-like domain, a stalk domain or region, CD8 α transmembrane domain, and a CD8 α cytoplasmic domain.

[00432] In embodiments CD8 polypeptides described herein may comprise (a) an immunoglobulin (Ig)-like domain comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 98%, at least about 99%, or about 100% sequence identity to the amino acid sequence of SEQ ID NO: 1; (b) a region comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 98%, at least about 99%, or about 100% sequence identity to the amino acid sequence of SEQ ID NO: 2; (c) a transmembrane domain comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 98%, at least about 99%, or about 100% sequence identity to the amino acid sequence of SEQ ID NO: 3, and (d) a cytoplasmic domain comprising at least about 80%, at least about 85%, at least about 90%,

at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 98%, at least about 99%, or about 100% sequence identity to the amino acid sequence of SEQ ID NO: 4. The CD8 polypeptides described herein may be co-expressed with a T-cell receptor or CAR-T in a T-cell and used in methods of adoptive cell therapy (ACT). The T-cell may be an $\alpha\beta$ T-cell or a $\gamma\delta$ T-cell.

[00433] In embodiments, CD8 polypeptides described herein may comprise (a) at least about 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 1; (b) at least about 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 2; (c) at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or about 100% sequence identity to the amino acid sequence of SEQ ID NO: 3, and (d) a at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or about 100% sequence identity to the amino acid sequence of SEQ ID NO: 4. The CD8 polypeptides described herein may be co-expressed with a T-cell receptor or CAR-T in a T-cell and used in methods of adoptive cell therapy (ACT). The T-cell may be an $\alpha\beta$ T-cell or a $\gamma\delta$ T-cell.

[00434] In embodiments, CD8 polypeptides described herein may comprise (a) SEQ ID NO: 1 comprising one, two, three, four, or five amino acid substitutions; (b) SEQ ID NO: 2 comprising one, two, three, four, or five amino acid substitutions; (c) SEQ ID NO: 3 comprising one, two, three, four, or five amino acid substitutions, and (d) SEQ ID NO: 4 comprising one, two, three, four, or five amino acid substitutions. In embodiments the substitutions are conservative amino acid substitutions. The CD8 polypeptides described herein may be co-expressed with a T-cell receptor or CAR-T in a T-cell and used in methods of adoptive cell therapy (ACT). The T-cell may be an $\gamma\delta$ T-cell or a $\gamma\delta$ T-cell.

[00435] CD8 is a membrane-anchored glycoprotein that functions as a coreceptor for antigen recognition of the peptide/MHC class I complexes by T cell receptors (TCR) and plays an important role in T cell development in the thymus and T cell activation in the periphery. Functional CD8 is a dimeric protein made of either two α chains (CD8 $\alpha\alpha$) or an α chain and a β chain (CD8 $\alpha\beta$), and the surface expression of the β chain may require its association with the coexpressed α chain to form the CD8 $\alpha\beta$ heterodimer. CD8 $\alpha\alpha$ and CD8 $\alpha\beta$ may be differentially expressed on a variety of lymphocytes. CD8 $\alpha\beta$ is expressed predominantly on the surface of $\alpha\beta$ TCR⁺ T cells and thymocytes, and CD8 $\alpha\alpha$ on a subset of $\alpha\beta$ TCR⁺, $\gamma\delta$ TCR⁺ intestinal intraepithelial lymphocytes, NK cells, dendritic cells, and a small fraction of CD4⁺ T cells.

[00436] For example, the human CD8 gene may express a protein of 235 amino acids. FIG. 1 shows a CD8 α protein (CD8 α 1 – SEQ ID NO: 258), which in an aspect is divided into the

following domains (starting at the amino terminal and ending at the carboxy terminal of the polypeptide): (1) signal peptide (amino acids -21 to -1), which may be cleaved off in human cells during the transport of the receptor to the cell surface and thus may not constitute part of the mature, active receptor; (2) immunoglobulin (Ig)-like domain (in this embodiment, amino acids 1-115), which may assume a structure, referred to as the immunoglobulin fold, which is similar to those of many other molecules involved in regulating the immune system, the immunoglobulin family of proteins. The crystal structure of the CD8 $\alpha\alpha$ receptor in complex with the human MHC molecule HLA-A2 has demonstrated how the Ig domain of CD8 $\alpha\alpha$ receptor binds the ligand; (3) membrane proximal region (in this embodiment, amino acids 116-160), which may be an extended linker region allowing the CD8 $\alpha\alpha$ receptor to "reach" from the surface of the T-cell over the top of the MHC to the $\alpha 3$ domain of the MHC where it binds. The stalk region may be glycosylated and may be inflexible; (4) transmembrane domain (in this embodiment, amino acids 161-188), which may anchor the CD8 $\alpha\alpha$ receptor in the cell membrane and is therefore not part of the soluble recombinant protein; and (5) cytoplasmic domain (in this embodiment, amino acids 189-214), which can mediate a signaling function in T-cells through its association with p56^{lck}, which may be involved in the T cell activation cascade of phosphorylation events. CD8 $\alpha 1$ (SEQ ID NO: 258) may be encoded by SEQ ID NO: 434.

[00437] CD8 α sequences may generally have a sufficient portion of the immunoglobulin domain to be able to bind to MHC. Generally, CD8 α molecules may contain all or a substantial part of immunoglobulin domain of CD8 α , e.g., SEQ ID NO: 258, but in an aspect may contain at least about 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110 or 115 amino acids of the immunoglobulin domain. The CD8 α molecules of the present disclosure may be dimers (e.g., CD8 $\alpha\alpha$ or CD8 $\alpha\beta$), and CD8 α monomer may be included within the scope of the present disclosure. In an aspect, CD8 α of the present disclosure may comprise CD8 $\alpha 1$ (SEQ ID NO: 258) and CD8 $\alpha 2$ (SEQ ID NO: 259). In an aspect, the present disclosure may comprise CD8 $\alpha 1$ (SEQ ID NO: 258) encoded by SEQ ID NO: 434.

[00438] CD8 α and β subunits may have similar structural motifs, including an Ig-like domain, a stalk region of 30–40 amino acids, a transmembrane region, and a short cytoplasmic domain of about 20 amino acids. CD8 α and β chains have two and one *N*-linked glycosylation sites, respectively, in the Ig-like domains where they share < 20% identity in their amino acid sequences. The CD8 β stalk region is 10–13 amino acids shorter than the CD8 α stalk and is highly glycosylated with *O*-linked carbohydrates. These carbohydrates on the β , but not the α , stalk region appear to be quite heterogeneous due to complex sialylations, which may be differentially regulated during the developmental stages of thymocytes and upon activation of T cells. Glycan adducts have been shown to play regulatory roles in the functions of glycoproteins

and in immune responses. Glycans proximal to transmembrane domains can affect the orientation of adjacent motifs. The unique biochemical properties of the CD8 β chain stalk region may present a plausible candidate for modulating the coreceptor function.

[00439] The CD8 α polypeptide may be modified by replacing CD8 α stalk region with a CD8 β stalk region to generate a modified CD8 α polypeptide. In embodiments the modified CD8 α polypeptides described herein may have a CD8 β stalk region comprising at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 2. The modified CD8 α polypeptides described herein may have an immunoglobulin (Ig)-like domain having at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 1. Modified CD8 polypeptides may have a transmembrane domain comprising at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 3. Modified CD8 polypeptides described herein may have a cytoplasmic tail comprising at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 4. The CD8 polypeptides described herein may have at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 5. The CD8 polypeptides described herein may comprise one or more signal peptide comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 99%, or about 100% sequence identity to the amino acid sequence of SEQ ID NO: 6 or SEQ ID NO: 294 directly or indirectly fused to the N-terminus or directly or indirectly fused to the C-terminus of mCD8 α polypeptide. The CD8 polypeptides described herein may have at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 7.

T-Cells

[00440] T-cells may express membrane-bound IL-15, the CD8 polypeptides described herein, or any combination thereof. As a non-limiting example, a T-cell may co-express a T-cell Receptor (TCR) and an IL-15/IL-15R α fusion polypeptide. As another non-limiting example, a T-cell may co-express a T-cell Receptor (TCR) and a modified CD8 polypeptide described herein. As another non-limiting example, a T-cell may co-express a T-cell Receptor (TCR), an

IL-15/IL-15R α fusion polypeptide, and a CD8 polypeptide described herein. T-cells may also express a chimeric antigen receptor (CAR), CAR-analogues, or CAR derivatives. In embodiments, a CD8 polypeptide may comprise a CD8 α chain and/or a CD8 β chain, and the CD8 α chain and/or CD8 β chain may independently be modified or unmodified.

[00441] The T-cell may be an $\alpha\beta$ T cell, a $\gamma\delta$ T cell, a natural killer T cell, or a combination thereof if in a population. The T cell may be a CD4 $^{+}$ T cell, CD8 $^{+}$ T cell, or a CD4 $^{+}$ /CD8 $^{+}$ T cell. In embodiments a cell may comprise an $\alpha\beta$ T cell, a $\gamma\delta$ T cell, a natural killer T cell, a CD4 $^{+}$ T cell, CD8 $^{+}$ T cell, a CD4 $^{+}$ /CD8 $^{+}$ cell, or any combination thereof.

[00442] A T cell may be an $\alpha\beta$ T cell and may express a CD8 polypeptide described herein. A T cell may be an $\alpha\beta$ T cell and may express a CD8 polypeptide described herein, for example, a modified CD8 α polypeptide or a CD8 α polypeptide with a CD8 β stalk region, e.g., m1CD8 α in Constructs #11 and #12 (FIG. 4) and CD8 α^{*} (FIG. 55B). A T cell may be an $\alpha\beta$ T cell and may express one or any combination of an IL-15 polypeptide, an IL-15R α polypeptide, an IL-15/IL-15R α fusion polypeptide, a CD8 polypeptide, and/or a CAR. In embodiments, a CD8 polypeptide may comprise a CD8 α chain and/or a CD8 β chain, and the CD8 α chain and/or CD8 β chain may independently be modified or unmodified.

[00443] A T cell may be a $\gamma\delta$ T cell and may express a CD8 polypeptide described herein and/or a membrane-bound IL-15 as described herein. In embodiments, a CD8 polypeptide may comprise a CD8 α chain and/or a CD8 β chain, and the CD8 α chain and/or CD8 β chain may independently be modified or unmodified. In embodiments a T cell may be a $\gamma\delta$ T cell and may express a CD8 polypeptide described herein, for example, a modified CD8 α polypeptide or a modified CD8 α polypeptide with a CD8 β stalk region, e.g., m1CD8 α in Constructs #11 and #12 (FIG. 4) and CD8 α^{*} (FIG. 55B). A T cell may be a $\gamma\delta$ T cell and may express one or any combination of an IL-15 polypeptide, an IL-15R α polypeptide, an IL-15/IL-15R α fusion polypeptide, a CD8 polypeptide, and/or a CAR. In embodiments, a CD8 polypeptide may comprise a CD8 α chain and/or a CD8 β chain, and the CD8 α chain and/or CD8 β chain may independently be modified or unmodified.

[00444] A T cell or cells comprising, or comprising nucleic acid(s) encoding, one or any combination of a TCR comprising an α chain and a β chain, a TCR comprising a γ chain and a δ chain, a CAR, an IL-15 polypeptide, an IL-15R α polypeptide, a membrane-bound IL-15 (e.g., an IL-15/IL-15R α fusion polypeptide), and/or a CD8 polypeptide may be provided. In embodiments, a CD8 polypeptide may comprise a CD8 α chain and/or a CD8 β chain, and the CD8 α chain and/or CD8 β chain may independently be modified or unmodified.

[00445] A T cell or cells comprising, or comprising nucleic acid(s) encoding, one or any combination of a TCR comprising an α chain and a β chain, a membrane-bound IL-15 (e.g., an IL-15/IL-15R α fusion polypeptide), and

[00446] /or a CD8 polypeptide may be provided. A T cell or cells comprising, or comprising nucleic acid(s) encoding, one or any combination of a TCR comprising a γ chain and a δ chain, a membrane-bound IL-15 (e.g., an IL-15/IL-15R α fusion polypeptide), and/or a CD8 polypeptide may be provided. A T cell or cells comprising, or comprising nucleic acid(s) encoding, one or any combination of a CAR, a membrane-bound IL-15 (e.g., an IL-15/IL-15R α fusion polypeptide), and/or a CD8 polypeptide may be provided. In embodiments, a CD8 polypeptide may comprise a CD8 α chain and/or a CD8 β chain, and the CD8 α chain and/or CD8 β chain may independently be modified or unmodified.

[00447] A T cell or cells comprising, or comprising nucleic acid(s) encoding, a TCR comprising an α chain and a β chain, a membrane-bound IL-15 (e.g., an IL-15/IL-15R α fusion polypeptide), and/or a CD8 polypeptide may be provided. In embodiments a T cell or cells comprising, or comprising nucleic acid(s) encoding, a TCR comprising a γ chain and a δ chain, a membrane-bound IL-15 (e.g., an IL-15/IL-15R α fusion polypeptide), and/or a CD8 polypeptide may be provided. A T cell or cells comprising, or comprising nucleic acid(s) encoding, a CAR, a membrane-bound IL-15 (e.g., an IL-15/IL-15R α fusion polypeptide), and/or a CD8 polypeptide may be provided. In embodiments, a CD8 polypeptide may comprise a CD8 α chain and/or a CD8 β chain, and the CD8 α chain and/or CD8 β chain may independently be modified or unmodified.

[00448] A T cell or cells comprising, or comprising nucleic acid(s) encoding, a TCR comprising an α chain and a β chain and/or a membrane-bound IL-15 (e.g., an IL-15/IL-15R α fusion polypeptide) may be provided. A T cell or cells comprising, or comprising nucleic acid(s) encoding, a TCR comprising a γ chain and a δ chain and a membrane-bound IL-15 (e.g., an IL-15/IL-15R α fusion polypeptide) may be provided. A T cell or cells comprising, or comprising nucleic acid(s) encoding, a CAR and a membrane-bound IL-15 (e.g., an IL-15/IL-15R α fusion polypeptide) may be provided. In embodiments, a CD8 polypeptide may comprise a CD8 α chain and/or a CD8 β chain, and the CD8 α chain and/or CD8 β chain may independently be modified or unmodified.

[00449] A T cell or cells comprising, or comprising nucleic acid(s) encoding, a TCR comprising an α chain and a β chain, a membrane-bound IL-15 (e.g., an IL-15/IL-15R α fusion polypeptide), and/or a CD8 polypeptide may be provided. In embodiments a T cell or cells comprising, or comprising nucleic acid(s) encoding, a TCR comprising a γ chain and a δ chain, a

membrane-bound IL-15 (e.g., an IL-15/IL-15R α fusion polypeptide) and/or a CD8 polypeptide may be provided. A T cell or cells comprising, or comprising nucleic acid(s) encoding a CAR, a membrane-bound IL-15 (e.g., an IL-15/IL-15R α fusion polypeptide) and/or a CD8 polypeptide may be provided. In embodiments, a CD8 polypeptide may comprise a CD8 α chain and/or a CD8 β chain, and the CD8 α chain and/or CD8 β chain may independently be modified or unmodified.

Natural Killer (NK) Cells

[00450] Natural Killer (NK) cells may also be engineered and used in adoptive cell therapy (ACT). See, e.g., Morton LT, *et al.*, “T cell receptor engineering of primary NK cells to therapeutically target tumors and tumor immune evasion”, *J Immunother Cancer*, March 14, 2022;10:e003715, which is incorporated by reference herein in its entirety. In embodiments engineered NK cells are provided.

[00451] NK cells may express membrane-bound IL-15, the CD8 polypeptides described herein, or any combination thereof. As a non-limiting example, a NK cell may co-express a T-cell Receptor (TCR) and an IL-15/IL-15R α fusion polypeptide. As another non-limiting example, a NK cell may co-express a T-cell Receptor (TCR) and a modified CD8 polypeptide described herein. As another non-limiting example, a NK cell may co-express a T-cell Receptor (TCR), an IL-15/IL-15R α fusion polypeptide, and a CD8 polypeptide described herein. NK cells may also express a chimeric antigen receptor (CAR), CAR-analogues, or CAR derivatives. In embodiments, a CD8 polypeptide may comprise a CD8 α chain and/or a CD8 β chain, and the CD8 α chain and/or CD8 β chain may independently be modified or unmodified.

[00452] The NK cell may express a CD8 polypeptide described herein. A NK cell may express a CD8 polypeptide described herein, for example, a modified CD8 α polypeptide or a CD8 α polypeptide with a CD8 β stalk region, e.g., m1CD8 α in Constructs #11 and #12 (FIG. 4) and CD8 α^* (FIG. 55B). A NK cell may express one or any combination of an IL-15 polypeptide, an IL-15R α polypeptide, an IL-15/IL-15R α fusion polypeptide, a CD8 polypeptide, and/or a CAR. In embodiments, a CD8 polypeptide may comprise a CD8 α chain and/or a CD8 β chain, and the CD8 α chain and/or CD8 β chain may independently be modified or unmodified.

[00453] A NK cell or cells comprising, or comprising nucleic acid(s) encoding, one or any combination of a TCR comprising a α chain and a β chain, a TCR comprising a γ chain and a δ chain, a CAR, an IL-15 polypeptide, an IL-15R α polypeptide, a membrane-bound IL-15 (e.g., an IL-15/IL-15R α fusion polypeptide), and/or a CD8 polypeptide may be provided. In embodiments, a CD8 polypeptide may comprise a CD8 α chain and/or a CD8 β chain, and the CD8 α chain and/or CD8 β chain may independently be modified or unmodified.

[00454] A NK cell or cells comprising, or comprising nucleic acid(s) encoding, one or any combination of a TCR comprising an α chain and a β chain, a membrane-bound IL-15 (e.g., an IL-15/IL-15R α fusion polypeptide), and/or a CD8 polypeptide may be provided. A NK cell or cells comprising, or comprising nucleic acid(s) encoding, one or any combination of a TCR comprising a γ chain and a δ chain, a membrane-bound IL-15 (e.g., an IL-15/IL-15R α fusion polypeptide), and/or a CD8 polypeptide may be provided. A NK cell or cells comprising, or comprising nucleic acid(s) encoding, one or any combination of a CAR, a membrane-bound IL-15 (e.g., an IL-15/IL-15R α fusion polypeptide), and/or a CD8 polypeptide may be provided. In embodiments, a CD8 polypeptide may comprise a CD8 α chain and/or a CD8 β chain, and the CD8 α chain and/or CD8 β chain may independently be modified or unmodified.

[00455] A NK cell or cells comprising, or comprising nucleic acid(s) encoding, a TCR comprising an α chain and a β chain, a membrane-bound IL-15 (e.g., an IL-15/IL-15R α fusion polypeptide), and/or a CD8 polypeptide may be provided. In embodiments a NK cell or cells comprising, or comprising nucleic acid(s) encoding, a TCR comprising a γ chain and a δ chain, a membrane-bound IL-15 (e.g., an IL-15/IL-15R α fusion polypeptide), and/or a CD8 polypeptide may be provided. A NK cell or cells comprising, or comprising nucleic acid(s) encoding, a CAR, a membrane-bound IL-15 (e.g., an IL-15/IL-15R α fusion polypeptide), and/or a CD8 polypeptide may be provided. In embodiments, a CD8 polypeptide may comprise a CD8 α chain and/or a CD8 β chain, and the CD8 α chain and/or CD8 β chain may independently be modified or unmodified.

[00456] A NK cell or cells comprising, or comprising nucleic acid(s) encoding, a TCR comprising an α chain and a β chain and/or a membrane-bound IL-15 (e.g., an IL-15/IL-15R α fusion polypeptide) may be provided. A NK cell or cells comprising, or comprising nucleic acid(s) encoding, a TCR comprising a γ chain and a δ chain and a membrane-bound IL-15 (e.g., an IL-15/IL-15R α fusion polypeptide) may be provided. A NK cell or cells comprising, or comprising nucleic acid(s) encoding, a CAR and a membrane-bound IL-15 (e.g., an IL-15/IL-15R α fusion polypeptide) may be provided. In embodiments, a CD8 polypeptide may comprise a CD8 α chain and/or a CD8 β chain, and the CD8 α chain and/or CD8 β chain may independently be modified or unmodified.

[00457] A NK cell or cells comprising, or comprising nucleic acid(s) encoding, a TCR comprising an α chain and a β chain, a membrane-bound IL-15 (e.g., an IL-15/IL-15R α fusion polypeptide), and/or a CD8 polypeptide may be provided. In embodiments a NK cell or cells comprising, or comprising nucleic acid(s) encoding, a TCR comprising a γ chain and a δ chain, a membrane-bound IL-15 (e.g., an IL-15/IL-15R α fusion polypeptide) and/or a CD8 polypeptide

may be provided. A NK cell or cells comprising, or comprising nucleic acid(s) encoding a CAR, a membrane-bound IL-15 (e.g., an IL-15/IL-15R α fusion polypeptide) and/or a CD8 polypeptide may be provided. In embodiments, a CD8 polypeptide may comprise a CD8 α chain and/or a CD8 β chain, and the CD8 α chain and/or CD8 β chain may independently be modified or unmodified.

T-cell Receptors

[00458] A T-cell may co-express a T-cell receptor (TCR), antigen binding protein, or both, with IL-15/IL-15R α fusion polypeptides and/or CD8 polypeptides described herein, including, but are not limited to, those listed in Table 3 (SEQ ID NOs: 15-92). Further, a T-cell may express one or any combination of IL-15/IL-15R α fusion polypeptides, CD8 polypeptides described herein, TCRs, and antigen binding proteins described in U.S. Patent Application Publication No. 2017/0267738; U.S. Patent Application Publication No. 2017/0312350; U.S. Patent Application Publication No. 2018/0051080; U.S. Patent Application Publication No. 2018/0164315; U.S. Patent Application Publication No. 2018/0161396; U.S. Patent Application Publication No. 2018/0162922; U.S. Patent Application Publication No. 2018/0273602; U.S. Patent Application Publication No. 2019/0016801; U.S. Patent Application Publication No. 2019/0002556; U.S. Patent Application Publication No. 2019/0135914; U.S. Patent 10,538,573; U.S. Patent 10,626,160; U.S. Patent Application Publication No. 2019/0321478; U.S. Patent Application Publication No. 2019/0256572; U.S. Patent 10,550,182; U.S. Patent 10,526,407; U.S. Patent Application Publication No. 2019/0284276; U.S. Patent Application Publication No. 2019/0016802; U.S. Patent Application Publication No. 2019/0016803; U.S. Patent Application Publication No. 2019/0016804; U.S. Patent 10,583,573; U.S. Patent Application Publication No. 2020/0339652; U.S. Patent 10,537,624; U.S. Patent 10,596,242; U.S. Patent Application Publication No. 2020/0188497; U.S. Patent 10,800,845; U.S. Patent Application Publication No. 2020/0385468; U.S. Patent 10,527,623; U.S. Patent 10,725,044; U.S. Patent Application Publication No. 2020/0249233; U.S. Patent 10,702,609; U.S. Patent Application Publication No. 2020/0254106; U.S. Patent 10,800,832; U.S. Patent Application Publication No. 2020/0123221; U.S. Patent 10,590,194; U.S. Patent 10,723,796; U.S. Patent Application Publication No. 2020/0140540; U.S. Patent 10,618,956; U.S. Patent Application Publication No. 2020/0207849; U.S. Patent Application Publication No. 2020/0088726; and U.S. Patent Application Publication No. 2020/0384028; the contents of each of these publications and sequence listings described therein are herein incorporated by reference in their entireties. The T-cell may be a CD4⁺ cell, a CD8⁺ cell, a CD4⁺/CD8⁺ cell, an $\alpha\beta$ T cell, a $\gamma\delta$ T cell, or a natural killer T cell. In embodiments TCRs described herein may be single-chain TCRs or soluble TCRs. In

embodiments, a CD8 polypeptide may comprise a CD8 α chain and/or a CD8 β chain, and the CD8 α chain and/or CD8 β chain may independently be modified or unmodified.

[00459] Further, the TCRs that may be co-expressed with a membrane-bound IL-15 (e.g., an IL-15/IL-15R α fusion polypeptide) and/or CD8 polypeptides described herein in a T-cell may be TCRs comprised of an alpha chain (TCR α) and a beta chain (TCR β). In embodiments, a CD8 polypeptide may comprise a CD8 α chain and/or a CD8 β chain, and the CD8 α chain and/or CD8 β chain may independently be modified or unmodified. The TCR α chains and TCR β chains that may be used in TCRs may be selected from R11KEA (SEQ ID NO: 15 and 16, which may be encoded by SEQ ID NO: 72 and 73, respectively), R20P1H7 (SEQ ID NO: 17 and 18), R7P1D5 (SEQ ID NO: 19 and 20), R10P2G12 (SEQ ID NO: 21 and 22), R10P1A7 (SEQ ID NO: 23 and 24), R4P1D10 (SEQ ID NO: 25 and 26), R4P3F9 (SEQ ID NO: 27 and 28), R4P3H3 (SEQ ID NO: 29 and 30), R36P3F9 (SEQ ID NO: 31 and 32), R52P2G11 (SEQ ID NO: 33 and 34), R53P2A9 (SEQ ID NO: 35 and 36), R26P1A9 (SEQ ID NO: 37 and 38), R26P2A6 (SEQ ID NO: 39 and 40), R26P3H1 (SEQ ID NO: 41 and 42), R35P3A4 (SEQ ID NO: 43 and 44), R37P1C9 (SEQ ID NO: 45 and 46), R37P1H1 (SEQ ID NO: 47 and 48), R42P3A9 (SEQ ID NO: 49 and 50), R43P3F2 (SEQ ID NO: 51 and 52), R43P3G5 (SEQ ID NO: 53 and 54), R59P2E7 (SEQ ID NO: 55 and 56), R11P3D3 (SEQ ID NO: 57 and 58), R16P1C10 (SEQ ID NO: 59 and 60), R16P1E8 (SEQ ID NO: 61 and 62), R17P1A9 (SEQ ID NO: 63 and 64), R17P1D7 (SEQ ID NO: 65 and 66), R17P1G3 (SEQ ID NO: 67 and 68), R17P2B6 (SEQ ID NO: 69 and 70), R11P3D3KE (SEQ ID NO: 71 and 303), R39P1C12 (SEQ ID NO: 304 and 74), R39P1F5 (SEQ ID NO: 75 and 76), R40P1C2 (SEQ ID NO: 77 and 78), R41P3E6 (SEQ ID NO: 79 and 80), R43P3G4 (SEQ ID NO: 81 and 82), R44P3B3 (SEQ ID NO: 83 and 84), R44P3E7 (SEQ ID NO: 85 and 86), R49P2B7 (SEQ ID NO: 87 and 88), R55P1G7 (SEQ ID NO: 89 and 90), or R59P2A7 (SEQ ID NO: 91 and 92). The T-cell may be a $\alpha\beta$ T cell, $\gamma\delta$ T cell, or a natural killer T cell.

[00460] Table 1 shows examples of the peptides to which TCRs bind when the peptide is in a complex with an MHC molecule. (MHC molecules in humans may be referred to as HLA, human leukocyte-antigens).

Table 1: T-Cell Receptor and Peptides

TCR name	Peptide (SEQ ID NO:)
R20P1H7, R7P1D5, R10P2G12	KVLEHVVRV (SEQ ID NO: 215)
R10P1A7	KIQEILTQV (SEQ ID NO: 123)
R4P1D10, R4P3F9, R4P3H3	FLLDGSANV (SEQ ID NO: 238)
R36P3F9, R52P2G11, R53P2A9	ILQDQGFLV (SEQ ID NO: 193)

R26P1A9, R26P2A6, R26P3H1, R35P3A4, R37P1C9, R37P1H1, R42P3A9, R43P3F2, R43P3G5, R59P2E7	KVLEYVIKV (SEQ ID NO: 202)
R11KEA, R11P3D3, R16P1C10, R16P1E8, R17P1A9, R17P1D7, R17P1G3, R17P2B6, R11P3D3KE	SLLQHLIGL (SEQ ID NO: 147)
R39P1C12, R39P1F5, R40P1C2, R41P3E6, R43P3G4, R44P3B3, R44P3E7, R49P2B7, R55P1G7, R59P2A7	ALSVLRLAL (SEQ ID NO: 248)

Tumor Associated Antigens (TAA)

[00461] Tumor associated antigen (TAA) peptides may be used with the IL-15/IL-15R α fusion polypeptides and/or CD8 polypeptides constructs, methods and embodiments described herein. For example, the T-cell receptors (TCRs) described herein may specifically bind to the TAA peptide when bound to a human leukocyte antigen (HLA). This is also known as a major histocompatibility complex (MHC) molecule. The MHC-molecules of the human are also designated as human leukocyte-antigens (HLA).

[00462] Tumor associated antigen (TAA) peptides that may be used with the IL-15/IL-15R α fusion polypeptides and/or CD8 polypeptides described herein include, but are not limited to, those listed in Table 3 and those TAA peptides described in U.S. Patent Application Publication No. 2016/0187351; U.S. Patent Application Publication No. 2017/0165335; U.S. Patent Application Publication No. 2017/0035807; U.S. Patent Application Publication No. 2016/0280759; U.S. Patent Application Publication No. 2016/0287687; U.S. Patent Application Publication No. 2016/0346371; U.S. Patent Application Publication No. 2016/0368965; U.S. Patent Application Publication No. 2017/0022251; U.S. Patent Application Publication No. 2017/0002055; U.S. Patent Application Publication No. 2017/0029486; U.S. Patent Application Publication No. 2017/0037089; U.S. Patent Application Publication No. 2017/0136108; U.S. Patent Application Publication No. 2017/0101473; U.S. Patent Application Publication No. 2017/0096461; U.S. Patent Application Publication No. 2017/0165337; U.S. Patent Application Publication No. 2017/0189505; U.S. Patent Application Publication No. 2017/0173132; U.S. Patent Application Publication No. 2017/0296640; U.S. Patent Application Publication No. 2017/0253633; U.S. Patent Application Publication No. 2017/0260249; U.S. Patent Application Publication No. 2018/0051080; U.S. Patent Application Publication No. 2018/0164315; U.S. Patent Application Publication No. 2018/0291082; U.S. Patent Application Publication No. 2018/0291083; U.S. Patent Application Publication No. 2019/0255110; U.S. Patent No.

9,717,774; U.S. Patent No. 9,895,415; U.S. Patent Application Publication No. 2019/0247433; U.S. Patent Application Publication No. 2019/0292520; U.S. Patent Application Publication No. 2020/0085930; U.S. Patent 10,336,809; U.S. Patent No. 10,131,703; U.S. Patent No. 10,081,664; U.S. Patent No. 10,081,664; U.S. Patent No. 10,093,715; U.S. Patent No. 10,583,573; and U.S. Patent Application Publication No. 2020/00085930; the contents of each of these publications, sequences, and sequence listings described therein are herein incorporated by reference in their entireties. The Tumor associated antigen (TAA) peptides described herein may be bound to an HLA (MHC molecule). The Tumor associated antigen (TAA) peptides bound to an HLA may be recognized by a TCR described herein, optionally co-expressed with CD8 polypeptides described herein.

[00463] T cells may be engineered to express a chimeric antigen receptor (CAR) comprising a ligand binding domain derived from NKG2D, NKG2A, NKG2C, NKG2F, LLT1, AICL, CD26, NKRP1, NKp30, NKp44, NKp46, CD244 (2B4), DNAM-1, and NKp80, or an anti-tumor antibody such as anti-Her2neu or anti-EGFR and a signaling domain obtained from CD3- ζ , Dap 10, CD28, 4-1BB, and CD40L. In some examples, the chimeric receptor binds MICA, MICB, Her2neu, EGFR, mesothelin, CD38, CD20, CD 19, PSA, RON, CD30, CD22, CD37, CD38, CD56, CD33, CD30, CD138, CD123, CD79b, CD70, CD75, CA6, GD2, alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), CEACAM5, CA-125, MUC-16, 5T4, NaPi2b, ROR1, ROR2, 5T4, PLIF, Her2/Neu, EGFRvIII, GPMNB, LIV-1, glycolipidF77, fibroblast activating protein, PSMA, STEAP-1, STEAP-2, c-met, CSPG4, Nectin-4, VEGFR2, PSCA, folate binding protein/receptor, SLC44A4, Cripto, CTAG1B, AXL, IL-13R, IL-3R, SLTRK6, gp100, MART1, Tyrosinase, SSX2, SSX4, NYESO-1, epithelial tumor antigen (ETA), MAGEA family genes (such as MAGE3A, MAGE4A), KKLC1, mutated ras, β raf, p53, MHC class I chain-related molecule A (MICA), or MHC class I chain-related molecule B (MICB), HPV, or CMV. The T-cell may be a $\alpha\beta$ T cell, $\gamma\delta$ T cell, or a natural killer T cell.

Culturing T-Cells

[00464] Methods for the activation, transduction, and/or expansion of T cells, e.g., tumor-infiltrating lymphocytes, CD8⁺ T cells, CD4⁺ T cells, and T cells, that may be used for transgene expression are described herein. T cells may be activated, transduced, and expanded, while depleting α - and/or β -TCR positive cells. The T-cell may be a $\alpha\beta$ T cell, $\gamma\delta$ T cell, or a natural killer T cell.

[00465] Methods for the *ex vivo* expansion of a population of engineered $\gamma\delta$ T-cells for adoptive transfer therapy are described herein. Engineered $\gamma\delta$ T cells of the disclosure may be expanded *ex vivo*. Engineered T cells described herein can be expanded *in vitro* without

activation by APCs, or without co-culture with APCs, and aminophosphates. Methods for transducing T cells are described in U.S. Patent Application No. Patent Application No. 2019/0175650, published on June 13, 2019, the contents of which are incorporated by reference in their entirety. Other methods for transduction and culturing of T-cells may be used.

[00466] T cells, including $\gamma\delta$ T cells, may be isolated from a complex sample that is cultured *in vitro*. In embodiments whole PBMC population, without prior depletion of specific cell populations, such as monocytes, $\alpha\beta$ T-cells, B-cells, and NK cells, can be activated and expanded. In embodiments enriched T cell populations can be generated prior to their specific activation and expansion. In embodiments activation and expansion of $\gamma\delta$ T cells may be performed with or without the presence of native or engineered antigen presenting cells (APCs). In embodiments, isolation and expansion of T cells from tumor specimens can be performed using immobilized T cell mitogens, including antibodies specific to $\gamma\delta$ TCR, and other $\gamma\delta$ TCR activating agents, including lectins. In embodiments isolation and expansion of $\gamma\delta$ T cells from tumor specimens can be performed in the absence of $\gamma\delta$ T cell mitogens, including antibodies specific to $\gamma\delta$ TCR, and other $\gamma\delta$ TCR activating agents, including lectins.

[00467] T cells, including $\gamma\delta$ T cells, may be isolated from leukapheresis of a subject, for example, a human subject. In embodiments $\gamma\delta$ T cells are not isolated from peripheral blood mononuclear cells (PBMC). The T cells may be isolated using anti-CD3 and anti-CD28 antibodies, optionally with recombinant human Interleukin-2 (rhIL-2), *e.g.*, between about 50 and 150 U/mL rhIL-2.

[00468] The isolated T cells can rapidly expand in response to contact with one or more antigens. Some $\gamma\delta$ T cells, such as V γ 9V δ 2⁺ T cells, can rapidly expand *in vitro* in response to contact with some antigens, like prenyl-pyrophosphates, alkyl amines, and metabolites or microbial extracts during tissue culture. Stimulated T-cells can exhibit numerous antigen-presentation, co-stimulation, and adhesion molecules that can facilitate the isolation of T-cells from a complex sample. T cells within a complex sample can be stimulated *in vitro* with at least one antigen for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, or another suitable period of time. Stimulation of T cells with a suitable antigen can expand T cell population *in vitro*.

[00469] Activation and expansion of $\gamma\delta$ T cells can be performed using activation and co-stimulatory agents described herein to trigger specific $\gamma\delta$ T cell proliferation and persistence populations. In embodiments activation and expansion of $\gamma\delta$ T-cells from different cultures can achieve distinct clonal or mixed polyclonal population subsets. In embodiments different agonist agents can be used to identify agents that provide specific $\gamma\delta$ activating signals. In embodiments agents that provide specific $\gamma\delta$ activating signals can be different monoclonal antibodies (MAbs) directed against the $\gamma\delta$ TCRs. In embodiments companion co-stimulatory agents to assist in

triggering specific $\gamma\delta$ T cell proliferation without induction of cell energy and apoptosis can be used. These co-stimulatory agents can include ligands binding to receptors expressed on $\gamma\delta$ cells, such as NKG2D, CD161, CD70, JAML, DNAX accessory molecule-1 (DNAM-1), ICOS, CD27, CD137, CD30, HVEM, SLAM, CD122, DAP, and CD28. In embodiments co-stimulatory agents can be antibodies specific to unique epitopes on CD2 and CD3 molecules. CD2 and CD3 can have different conformation structures when expressed on $\alpha\beta$ or $\gamma\delta$ T-cells. In embodiments specific antibodies to CD3 and CD2 can lead to distinct activation of $\gamma\delta$ T cells.

[00470] Non-limiting examples of antigens that may be used to stimulate the expansion of T cells, including $\gamma\delta$ T cells, from a complex sample in vitro may comprise, prenyl-pyrophosphates, such as isopentenyl pyrophosphate (IPP), alkyl-amines, metabolites of human microbial pathogens, metabolites of commensal bacteria, methyl-3-butenyl-1-pyrophosphate (2M3B1PP), (E)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate (HMB-PP), ethyl pyrophosphate (EPP), farnesyl pyrophosphate (FPP), dimethylallyl phosphate (DMAP), dimethylallyl pyrophosphate (DMAPP), ethyl-adenosine triphosphate (EPPPA), geranyl pyrophosphate (GPP), geranylgeranyl pyrophosphate (GGPP), isopentenyl-adenosine triphosphate (IPPPA), monoethyl phosphate (MEP), monoethyl pyrophosphate (MEPP), 3-formyl-1-butyl-pyrophosphate (TUBAg 1), X-pyrophosphate (TUBAg 2), 3-formyl-1-butyl-uridine triphosphate (TUBAg 3), 3-formyl-1-butyl-deoxythymidine triphosphate (TUBAg 4), monoethyl alkylamines, allyl pyrophosphate, crotyl pyrophosphate, dimethylallyl- γ -uridine triphosphate, crotyl- γ -uridine triphosphate, allyl- γ -uridine triphosphate, ethylamine, isobutylamine, sec-butylamine, iso-amylamine and nitrogen containing bisphosphonates.

[00471] A population of T-cells, including $\gamma\delta$ T cells, may be expanded *ex vivo* prior to engineering of the T-cells. Non-limiting example of reagents that can be used to facilitate the expansion of a T-cell population in vitro may comprise anti-CD3 or anti-CD2, anti-CD27, anti-CD30, anti-CD70, anti-OX40 antibodies, IL-2, IL-15, IL-12, IL-9, IL-33, IL-18, or IL-21, CD70 (CD27 ligand), phytohaemagglutinin (PHA), concavalin A (ConA), pokeweed (PWM), protein peanut agglutinin (PNA), soybean agglutinin (SBA), Les Culinaris Agglutinin (LCA), Pisum Sativum Agglutinin (PSA), Helix pomatia agglutinin (HPA), Vicia graminea Lectin (VGA), or another suitable mitogen capable of stimulating T-cell proliferation. Further, the T-cells may be expanded using MCSF, IL-6, eotaxin, IFN- α , IL-7, gamma-induced protein 10, IFN- γ , IL-1RA, IL-12, MIP-1 α , IL-2, IL-13, MIP-1 β , IL-2R, IL-15, and any combination thereof.

[00472] The ability of $\gamma\delta$ T cells to recognize a broad spectrum of antigens can be enhanced by genetic engineering of the $\gamma\delta$ T cells. The $\gamma\delta$ T cells can be engineered to provide a universal allogeneic therapy that recognizes an antigen of choice in vivo. Genetic engineering of the $\gamma\delta$ T-

cells may comprise stably integrating a construct expressing a tumor recognition moiety, such as $\alpha\beta$ TCR, $\gamma\delta$ TCR, chimeric antigen receptor (CAR), which combines both antigen-binding and T-cell activating functions into a single receptor, an antigen binding fragment thereof, or a lymphocyte activation domain into the genome of the isolated $\gamma\delta$ T-cell(s), a cytokine (for example, IL-15, IL-12, IL-2, IL-7, IL-21, IL-18, IL-19, IL-33, IL-4, IL-9, IL-23, or IL-1 β) to enhance T-cell proliferation, survival, and function *ex vivo* and *in vivo*. Genetic engineering of the isolated $\gamma\delta$ T-cell may also include deleting or disrupting gene expression from one or more endogenous genes in the genome of the isolated $\gamma\delta$ T-cells, such as the MHC locus (loci).

[00473] Engineered (or transduced) T cells, including $\gamma\delta$ T cells, can be expanded *ex vivo* without stimulation by an antigen presenting cell or aminobisphosphonate. Antigen reactive engineered T cells of the present disclosure may be expanded *ex vivo* and *in vivo*. In embodiments an active population of engineered T cells may be expanded *ex vivo* without antigen stimulation by an antigen presenting cell, an antigenic peptide, a non-peptide molecule, or a small molecule compound, such as an aminobisphosphonate but using certain antibodies, cytokines, mitogens, or fusion proteins, such as IL-17 Fc fusion, MICA Fc fusion, and CD70 Fc fusion. Examples of antibodies that can be used in the expansion of a $\gamma\delta$ T-cell population include anti-CD3, anti-CD27, anti-CD30, anti-CD70, anti-OX40, anti-NKG2D, or anti-CD2 antibodies, examples of cytokines may comprise IL-2, IL-15, IL-12, IL-21, IL-18, IL-9, IL-7, and/or IL-33, and examples of mitogens may comprise CD70 the ligand for human CD27, phytohaemagglutinin (PHA), concavalin A (ConA), pokeweed mitogen (PWM), protein peanut agglutinin (PNA), soybean agglutinin (SBA), les culinaris agglutinin (LCA), pisum sativum agglutinin (PSA), Helix pomatia agglutinin (HPA), Vicia graminea Lectin (VGA) or another suitable mitogen capable of stimulating T-cell proliferation.

[00474] A population of engineered T cells, including $\gamma\delta$ T cells, can be expanded in less than about 60 days, less than about 48 days, less than about 36 days, less than about 24 days, less than about 12 days, or less than about 6 days. In embodiments a population of engineered T cells can be expanded from about 7 days to about 49 days, about 7 days to about 42 days, from about 7 days to about 35 days, from about 7 days to about 28 days, from about 7 days to about 21 days, or from about 7 days to about 14 days. The T-cells may be expanded for between about 1 and about 21 days. For example, the T-cells may be expanded for about at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 days.

[00475] In embodiments the same methodology may be used to isolate, activate, and expand $\alpha\beta$ T cells.

[00476] In embodiments the same methodology may be used to isolate, activate, and expand $\gamma\delta$ T cells.

Vectors

[00477] Engineered cells may be generated using various methods, including those recognized in the literature. For example, a polynucleotide encoding an expression cassette that comprises a tumor recognition, or another type of recognition moiety, can be stably introduced into the T-cell by a transposon/transposase system or a viral-based gene transfer system, such as a lentiviral or a retroviral system, or another suitable method, such as transfection, electroporation, transduction, lipofection, calcium phosphate (CaPO₄), nanoengineered substances, such as Ormosil, viral delivery methods, including adenoviruses, retroviruses, lentiviruses, adeno-associated viruses, or another suitable method. A number of viral methods have been used for human gene therapy, such as the methods described in WO 1993/020221, the content of which is incorporated herein in its entirety. Non-limiting examples of viral methods that can be used to engineer cells may comprise γ -retroviral, adenoviral, lentiviral, herpes simplex virus, vaccinia virus, pox virus, or adeno-virus associated viral methods. A cell may comprise an $\alpha\beta$ T cell, a $\gamma\delta$ T cell, a natural killer cell, a natural killer T cell, a CD4⁺ T cell, CD8⁺ T cell, a CD4⁺/CD8⁺ cell, or any combination thereof.

[00478] Viruses used for transfection of cells include naturally occurring viruses as well as artificial viruses. Viruses may be either an enveloped or non-enveloped virus. Parvoviruses (such as AAVs) are examples of non-enveloped viruses. The viruses may be enveloped viruses. The viruses used for transfection of cells may be retroviruses and in particular lentiviruses. Viral envelope proteins that can promote viral infection of eukaryotic cells may comprise HIV-1 derived lentiviral vectors (LVs) pseudotyped with envelope glycoproteins (GPs) from the vesicular stomatitis virus (VSV-G), the modified feline endogenous retrovirus (RD114TR) (SEQ ID NO: 97), and the modified gibbon ape leukemia virus (GALVTR). These envelope proteins can efficiently promote entry of other viruses, such as parvoviruses, including adeno-associated viruses (AAV), thereby demonstrating their broad efficiency. For example, other viral envelop proteins may be used including Moloney murine leukemia virus (MLV) 4070 env (such as described in Merten et al., *J. Virol.* 79:834-840, 2005; the content of which is incorporated herein by reference), RD114 env, chimeric envelope protein RD114pro or RDpro (which is an RD114-HIV chimera that was constructed by replacing the R peptide cleavage sequence of RD114 with the HIV-1 matrix/capsid (MA/CA) cleavage sequence, such as described in Bell et al. *Experimental Biology and Medicine* 2010; 235: 1269–1276; the content of which is incorporated herein by reference), baculovirus GP64 env (such as described in Wang et al. *J. Virol.* 81:10869-10878, 2007; the content of which is incorporated herein by reference), or GALV env (such as described in Merten et al., *J. Virol.* 79:834-840, 2005; the content of which is incorporated herein by reference), or derivatives thereof.

[00479] A single lentiviral cassette can be used to create a single lentiviral vector, expressing at least four individual monomer proteins of two distinct dimers from a single multi-cistronic mRNA so as to co-express the dimers on the cell surface. For example, the integration of a single copy of the lentiviral vector was sufficient to transform T cells to co-express TCR $\alpha\beta$ and CD8 $\alpha\beta$, optionally $\alpha\beta$ T cells or $\gamma\delta$ T cells.

[00480] Vectors may comprise a multi-cistronic cassette within a single vector capable of expressing more than one, more than two, more than three, more than four genes, more than five genes, or more than six genes, in which the polypeptides encoded by these genes may interact with one another or may form dimers. The dimers may be homodimers, *e.g.*, two identical proteins forming a dimer, or heterodimers, *e.g.*, two structurally different proteins forming a dimer.

[00481] Additionally, multiple vectors may be used to transfect cells with the constructs and sequences described herein. One or more vectors may comprise any combination of TCR transgene(s), IL-15/IL-15R α fusion polypeptide transgene(s), and CD8 transgene(s) in any order. As a non-limiting example, a first vector may comprise a transgene encoding a TCR, a second vector may comprise a transgene encoding an IL-15/IL-15R α fusion polypeptide, and a third vector may comprise a transgene encoding a CD8 a polypeptide described herein, and the vectors may be transfected into cells either simultaneously or sequentially in any order, using recognized methods. As another non-limiting example, a single vector may encode two transgenes in any order, or a single vector may encode three or more transgenes in any order. As another non-limiting example, a cell line that is stably transfected with one or more transgene(s) may then be transfected with one or more other transgene(s).

[00482] One or more vector may comprise a nucleic acid encoding a membrane-bound IL-15 (*e.g.*, an IL-15/IL-15R α fusion polypeptide). One or more vector may comprise a nucleic acid encoding a CD8 polypeptide. One or more vector may comprise a nucleic acid encoding a CD8 α polypeptide. One or more vector may comprise a nucleic acid encoding a CD8 β polypeptide.

[00483] One or more vector may comprise a nucleic acid encoding a T cell receptor (TCR) comprising an α chain and a β chain. One or more vector may comprise a nucleic acid encoding a T cell receptor (TCR) comprising an γ chain and a δ chain. One or more vector may comprise a nucleic acid encoding a chimeric antigen receptor (CAR).

[00484] More than one vector may comprise a nucleic acid or nucleic acids encoding one or any combination of an IL-15 polypeptide, an IL-15R α polypeptide, a membrane-bound IL-15 (*e.g.*, an IL-15/IL-15R α fusion polypeptide), a CD8 polypeptide, a TCR comprising an α chain and a β chain, a TCR comprising an γ chain and a δ chain, and/or a CAR. In embodiments, a

CD8 polypeptide may comprise a CD8 α chain and/or a CD8 β chain, and the CD8 α chain and/or CD8 β chain may independently be modified or unmodified.

[00485] A single vector may comprise a nucleic acid or nucleic acids encoding one or any combination of an IL-15 polypeptide, an IL-15R α polypeptide, a membrane-bound IL-15 (e.g., an IL-15/IL-15R α fusion polypeptide), a CD8 polypeptide, a TCR comprising an α chain and a β chain, a TCR comprising an γ chain and a δ chain, and/or a CAR. In embodiments, a CD8 polypeptide may comprise a CD8 α chain and/or a CD8 β chain, and the CD8 α chain and/or CD8 β chain may independently be modified or unmodified.

[00486] As used herein, the term “cistron” refers to a section of a nucleic acid molecule that specifies the formation of one polypeptide chain, i.e. coding for one polypeptide chain. For example, “mono-cistron” refers to one section of a nucleic acid molecule that specifies the formation of one polypeptide chain, i.e. coding for one polypeptide chain; “bi-cistron” refers to two sections of a nucleic acid molecule that specify the formation of two polypeptide chains, i.e. coding for two polypeptide chains; “tri-cistron” refers to three sections of a nucleic acid molecule that specify the formation of three polypeptide chains, i.e. coding for three polypeptide chains; etc.; “multicistron” refers two or more sections of a nucleic acid molecule that specify the formation of two or more polypeptide chains, i.e. coding for two or more polypeptide chains.

[00487] As used herein, the term “arranged in tandem” refers to the arrangement of the genes contiguously, one following or behind the other, in a single file on a nucleic acid sequence. The genes are ligated together contiguously on a nucleic acid sequence, with the coding strands (sense strands) of each gene ligated together on a nucleic acid sequence.

[00488] A transgene may further include one or more multicistronic element(s) and the multicistronic element(s) may be positioned, as non-limiting examples, between any, some, or each of a nucleic acid encoding a TCR α or a portion thereof, a nucleic acid encoding a TCR β or a portion thereof, a nucleic acid encoding a CD8 α or a portion thereof, a nucleic acid encoding a CD8 β or a portion thereof, and/or a nucleic acid encoding a IL-15/IL-15R α fusion polypeptide or a portion thereof. The multicistronic element(s) may be positioned, as non-limiting examples, between any two nucleic acid sequences encoding of TCR α , TCR β , CD8 α , CD8 β , and/or a membrane-bound IL-15 (e.g., an IL-15/IL-15R α fusion polypeptide), and these coding sequences may be in any order. The multicistronic element(s) may include a sequence encoding a ribosome skip element selected from among a T2A, a P2A, a E2A or a F2A or an internal ribosome entry site (IRES).

[00489] As used herein, the term “self-cleaving 2A peptide” refers to relatively short peptides (of the order of 20 amino acids long, depending on the virus of origin) acting co-translationally, by preventing the formation of a normal peptide bond between the glycine and last proline,

resulting in the ribosome skipping to the next codon, and the nascent peptide cleaving between the Gly and Pro. After cleavage, the short 2A peptide remains directly or indirectly fused to the C-terminus of the ‘upstream’ protein, while the proline is added to the N-terminus of the ‘downstream’ protein. Self-cleaving 2A peptide may be selected from porcine teschovirus-1 (P2A), equine rhinitis A virus (E2A), *Thossea asigna* virus (T2A), foot-and-mouth disease virus (F2A), or any combination thereof (see, e.g., Kim et al., PLOS One 6:e18556, 2011, the content of which including 2A nucleic acid and amino acid sequences are incorporated herein by reference in their entirety). By adding one or more linker sequences (such as, but not limited to, GSG, LE, SGSG (SEQ ID NO: 266), or the linkers set forth in SEQ ID NO: 383, 385, 387, 389, 393, 396-432) before the self-cleaving 2A sequence, this may enable efficient synthesis of biologically active proteins, e.g., TCRs.

[00490] As used herein, the term “internal ribosome entry site (IRES)” refers to a nucleotide sequence located in a messenger RNA (mRNA) sequence, which can initiate translation without relying on the 5' cap structure. IRES is usually located in the 5' untranslated region (5'UTR) but may also be located in other positions of the mRNA. In embodiments IRES may be selected from IRES from viruses, IRES from cellular mRNAs, in particular IRES from picornavirus, such as polio, EMCV and FMDV, flavivirus, such as hepatitis C virus (HCV), pestivirus, such as classical swine fever virus (CSFV), retrovirus, such as murine leukemia virus (MLV), lentivirus, such as simian immunodeficiency virus (SIV), and insect RNA virus, such as cricket paralysis virus (CRPV), and IRES from cellular mRNAs, e.g. translation initiation factors, such as eIF4G, and DAP5, transcription factors, such as c-Myc, and NF- κ B-repressing factor (NRF), growth factors, such as vascular endothelial growth factor (VEGF), fibroblast growth factor 2 (FGF-2), platelet-derived growth factor B (PDGF-B), homeotic genes, such as antennapedia, survival proteins, such as X-linked inhibitor of apoptosis (XIAP), and Apaf-1, and other cellular mRNA, such as BiP.

[00491] Constructs and vectors described herein may be used with the methodology described in U.S. Patent Application Publication No. 2019/0175650, published on June 13, 2019, the contents of which are incorporated by reference in their entirety.

[00492] In embodiments a vector may further comprise a post-transcriptional regulatory element (PRE) sequence. In embodiments the post-transcriptional regulatory element (PRE) sequence may be selected from a Woodchuck hepatitis virus PRE (WPRE) (such as, but not limited to wild type WPRE, such as but not limited to SEQ ID NO: 264, or a mutated WPRE, such as but not limited to WPREmut1 (SEQ ID NO: 256) or WPREmut2 (SEQ ID NO: 257)) or a hepatitis B virus (HBV) PRE (HPRE) (SEQ ID NO: 437), variant(s) thereof, or any combination thereof.

[00493] In embodiments a vector may further comprise one or more promoter. In embodiments the promoter(s) may be selected from cytomegalovirus (CMV) promoter, phosphoglycerate kinase (PGK) promoter, myelin basic protein (MBP) promoter, glial fibrillary acidic protein (GFAP) promoter, modified MoMuLV LTR comprising myeloproliferative sarcoma virus enhancer (MNDU3), Ubiquitin C promoter, EF-1 alpha promoter, Murine Stem Cell Virus (MSCV) promoter, the promoter from CD69, nuclear factor of activated T-cells (NFAT) promoter, IL-2 promoter, minimal IL-2 promoter, or a combination thereof.

[00494] In embodiments a vector may comprise one or more Kozak sequence. In embodiments, the Kozak sequence may initiate, increase, or facilitate translation, or a combination thereof. In embodiments, the Kozak sequence may be GCCACC. In embodiments, the Kozak sequence may be ACCATGG. In embodiments, the Kozak sequence may be GCCNCCATGG, where N is a purine (A or G) (SEQ ID NO: 382).

[00495] In embodiments a vector may comprise one or more Factor Xa sites.

[00496] In embodiments a vector may comprise one or more enhancer. In embodiments the enhancer may comprise Conserved Non-Coding Sequence (CNS) 0, CNS 1, CNS2, CNS 3, CNS 4, or portions or any combination thereof.

[00497] In embodiments a vector may be a viral vector or a non-viral vector.

[00498] In embodiments a vector may be selected from adenoviruses, poxviruses, alphaviruses, arenaviruses, flaviviruses, rhabdoviruses, retroviruses, lentiviruses, herpesviruses, paramyxoviruses, picornaviruses, or a combination thereof.

[00499] In embodiments a vector may be pseudotyped with an envelope protein of a virus selected from the native feline endogenous virus (RD114), a chimeric version of RD114 (RD114TR), gibbon ape leukemia virus (GALV), a chimeric version of GALV (GALV-TR), amphotropic murine leukemia virus (MLV 4070A), baculovirus (GP64), vesicular stomatitis virus (VSV-G), fowl plague virus (FPV), Ebola virus (EboV), or baboon retroviral envelope glycoprotein (BaEV), lymphocytic choriomeningitis virus (LCMV), or a combination thereof.

[00500] Non-viral vectors may also be used with the sequences, constructs, and cells described herein.

[00501] Cells may be transfected by other means known in the art including lipofection (liposome-based transfection), electroporation, calcium phosphate transfection, biolistic particle delivery (*e.g.*, gene guns), microinjection, or any combination thereof. Various methods of transfecting cells are known in the art. *See, e.g.*, Sambrook & Russell (Eds.) *Molecular Cloning: A Laboratory Manual* (3rd Ed.) Volumes 1–3 (2001) Cold Spring Harbor Laboratory Press; Ramamoorth & Narvekar “Non Viral Vectors in Gene Therapy- An Overview.” *J Clin Diagn Res.* (2015) 9(1): GE01–GE06.

Gene Editing

[00502] In embodiments, transgenes (e.g., transgene(s) encoding CD8 α chain and/or β chain, transgene(s) encoding TCR α chain and/or β chain, and/or transgene(s) encoding membrane-bound IL-15, e.g., IL-15/IL-15R α fusion polypeptide) may be inserted into a cell(s) using gene addition, gene editing, gene replacement, and/or gene transfer techniques, such as but not limited to knock-in techniques, such as but not limited to targeted knock-in techniques. Cells may be, as non-limiting examples, T cells or natural killer cells or combinations thereof. T cells may be, as non-limiting examples, $\alpha\beta$ T cells, $\gamma\delta$ T cells, natural killer T cells, CD4⁺ cells, CD8⁺ cells, CD4⁺/CD8⁺ cells, or combinations thereof. As non-limiting examples, techniques such as Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) systems (using, as non-limiting examples, Cas9, Cas12, Cas12a, Cas12a2, and/or Cas13), transcription-activator-like effector nuclease (TALEN) systems, and/or transposon-based systems (see, e.g., US Patent Publication No. 2019/0169637, which is incorporated herein in its entirety). Non-limiting examples of transposon-based systems include Sleeping Beauty (see, e.g., US Patent Nos. 7,985,739; 6,613,752; and 9,228,180 and US Patent Publication Nos. 2005/0003542; 2004/0092471; 2002/0103152; 2016/0264949; 2018/0135032; 2011/0117072; 2019/0169638; 2005/0112764; 2017/0029774; 2021/0139583, each of which is incorporated herein in its entirety), piggyBac (see, e.g., US Patent Nos. 10,287,559; 11,186,847; 10,131,885; 9,546,382; 8,399,643; 8,592,211; 6,962,810; 7,105,343; and 6,551,825 and US Patent Publication Nos. 2018/0142219; 2017/0166874; 2016/0160235; 2020/0087635; 2018/0195086; 2013/0160152; 2010/0287633; 2022/0064610; 2009/0042297; 2002/0173634; and 2017/0226531, each of which is incorporated herein in its entirety), and/or TcBuster systems (see, e.g., US Patent Nos. 11,278,570; 11,162,084; and 11,111,483 and US Patent Publication Nos. 2021/0277366; 2020/0339965; and 2020/0323902, each of which is incorporated herein in its entirety)).

Compositions

[00503] Compositions may comprise a membrane-bound IL-15 (e.g., an IL-15/IL-15R α fusion polypeptide) and/or the CD8 polypeptides described herein. Further, compositions described herein may comprise a T-cell and/or a natural killer cell expressing a membrane-bound IL-15 (e.g., an IL-15/IL-15R α fusion polypeptide) and/or CD8 polypeptides described herein and/or a TCR as described herein. The compositions described herein may comprise a T-cell and/or a natural killer cell expressing a membrane-bound IL-15 (e.g., an IL-15/IL-15R α fusion polypeptide) and/or CD8 polypeptides described herein and a T-cell receptor (TCR), optionally a TCR that specifically binds one of the TAA described herein complexed with an antigen presenting protein, e.g., MHC, referred to as HLA in humans, for human leukocyte antigen. In

embodiments, a CD8 polypeptide may comprise a CD8 α chain and/or a CD8 β chain, and the CD8 α chain and/or CD8 β chain may independently be modified or unmodified.

[00504] To facilitate administration, the T cells and/or natural killer cells described herein can be made into a pharmaceutical composition or made into an implant appropriate for administration *in vivo*, with pharmaceutically acceptable carriers or diluents. The means of making such a composition or an implant are described in the art. *See, e.g.*, Remington's Pharmaceutical Sciences, 16th Ed., Mack, ed. (1980).

[00505] The T cells and/or natural killer cells described herein can be formulated into a preparation in semisolid or liquid form, such as a capsule, solution, infusion, or injection. Means known in the art can be utilized to prevent or minimize release and absorption of the composition until it reaches the target tissue or organ, or to ensure timed-release of the composition. Desirably, however, a pharmaceutically acceptable form is employed that does not hinder the cells from expressing the CARs or TCRs. Thus, desirably the T cells and/or natural killer cells described herein can be made into a pharmaceutical composition comprising a carrier. The T cells and/or natural killer cells described herein can be formulated with a physiologically acceptable carrier or excipient to prepare a pharmaceutical composition. The carrier and composition can be sterile. Carriers include, for example, a balanced salt solution, such as Hanks' balanced salt solution, or normal saline. The formulation should suit the mode of administration. Suitable pharmaceutically acceptable carriers include but are not limited to water, salt solutions (*e.g.*, NaCl), saline, buffered saline, as well as any combination thereof. The pharmaceutical preparations can, if desired, be mixed with auxiliary agents, *e.g.*, lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, that do not deleteriously react with the T-cells and/or natural killer cells. The cells may be $\alpha\beta$ T cells, $\gamma\delta$ T cells, and/or natural killer cells that express a membrane-bound IL-15 (*e.g.*, an IL-15/IL-15R α fusion polypeptide) and/or CD8 polypeptides described herein, optionally a TCR described herein. In embodiments, a CD8 polypeptide may comprise a CD8 α chain and/or a CD8 β chain, and the CD8 α chain and/or CD8 β chain may independently be modified or unmodified.

[00506] A composition of the present disclosure can be provided in unit dosage form wherein each dosage unit, *e.g.*, an injection, contains a predetermined amount of the composition, alone or in appropriate combination with other active agents.

[00507] The compositions described herein may be a pharmaceutical composition. Pharmaceutical composition described herein may further comprise an adjuvant selected from the group consisting of colony-stimulating factors, including but not limited to Granulocyte

Macrophage Colony Stimulating Factor (GM-CSF, sargramostim), cyclophosphamide, imiquimod, resiquimod, interferon-alpha, or a combination thereof.

[00508] Pharmaceutical compositions described herein may comprise an adjuvant selected from the group consisting of colony-stimulating factors, *e.g.*, Granulocyte Macrophage Colony Stimulating Factor (GM-CSF, sargramostim), cyclophosphamide, imiquimod and resiquimod.

[00509] Adjuvants include but are not limited to cyclophosphamide, imiquimod or resiquimod. Other adjuvants include Montanide IMS 1312, Montanide ISA 206, Montanide ISA 50V, Montanide ISA-51, poly-ICLC (Hiltonol®) and anti-CD40 mAB, or any combination thereof.

[00510] Other examples for useful adjuvants include, but are not limited to, chemically modified CpGs (*e.g.* CpR, Idera), dsRNA analogues such as Poly(I:C) and derivatives thereof (*e.g.* AmpliGen®, Hiltonol®, poly-(ICLC), poly(IC-R), poly(I:C12U), non-CpG bacterial DNA or RNA as well as immunoactive small molecules and antibodies such as cyclophosphamide, sunitinib, immune checkpoint inhibitors including ipilimumab, nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab, and cemiplimab, Bevacizumab®, celebrex, NCX-4016, sildenafil, tadalafil, vardenafil, sorafenib, temozolomide, temsirolimus, XL-999, CP-547632, pazopanib, VEGF Trap, ZD2171, AZD2171, anti-CTLA4, other antibodies targeting key structures of the immune system (*e.g.* anti-CD40, anti-TGFbeta, anti-TNFalpha receptor) and SC58175, which may act therapeutically and/or as an adjuvant. The amounts and concentrations of adjuvants and additives useful in the context of the present disclosure can readily be determined by the skilled artisan without undue experimentation.

[00511] Other adjuvants include but are not limited to anti-CD40, imiquimod, resiquimod, GM-CSF, cyclophosphamide, sunitinib, bevacizumab, atezolizumab, interferon-alpha, interferon-beta, CpG oligonucleotides and derivatives, poly-(I:C) and derivatives, RNA, sildenafil, and particulate formulations with poly(lactide co-glycolide) (PLG), Polyinosinic-polycytidylic acid-poly-l-lysine carboxymethylcellulose (poly-ICLC), virosomes, and/or interleukin-1 (IL-1), IL-2, IL-4, IL-7, IL-12, IL-13, IL-15, IL-18, IL-21, and IL-23. *See, e.g.*, Narayanan *et al.* J. Med. Chem. (2003) 46(23): 5031–5044; Pohar *et al.* Scientific Reports 7 14598 (2017); Grajkowski *et al.* Nucleic Acids Research (2005) 33(11): 3550–3560; Martins *et al.* Expert Rev Vaccines (2015) 14(3): 447–59.

[00512] The compositions described herein may also include one or more adjuvants. Adjuvants are substances that non-specifically enhance or potentiate the immune response (*e.g.*, immune responses mediated by CD8-positive T cells and helper-T (TH) cells to an antigen and would thus be considered useful in the medicament of the present disclosure). Suitable adjuvants include, but are not limited to, 1018 ISS, aluminum salts, AMPLIVAX®, AS15, BCG, CP-

870,893, CpG7909, CyaA, dSLIM, flagellin or TLR5 ligands derived from flagellin, FLT3 ligand, GM-CSF, IC30, IC31, Imiquimod (ALDARA®), resiquimod, ImuFact IMP321, Interleukins as IL-2, IL-13, IL-21, Interferon-alpha or -beta, or pegylated derivatives thereof, IS Patch, ISS, ISCOMATRIX, ISCOMs, JuvImmune®, LipoVac, MALP2, MF59, monophosphoryl lipid A, Montanide IMS 1312, Montanide ISA 206, Montanide ISA 50V, Montanide ISA-51, water-in-oil and oil-in-water emulsions, OK-432, OM-174, OM-197-MP-EC, ONTAK, OspA, PepTel® vector system, poly(lactide co-glycolide) [PLG]-based and dextran microparticles, talactoferrin SRL172, Virosomes and other Virus-like particles, YF-17D, VEGF trap, R848, beta-glucan, Pam3Cys, Aquila's QS21 stimulon, which is derived from saponin, mycobacterial extracts and synthetic bacterial cell wall mimics, and other proprietary adjuvants such as Ribi's Detox, Quil, or Superfos. Adjuvants such as Freund's or GM-CSF may be used, in embodiments. Several immunological adjuvants (e.g., MF59) specific for dendritic cells and their preparation have been described previously. Also, cytokines may be used. Several cytokines have been directly linked to influencing dendritic cell migration to lymphoid tissues (e.g., TNF-), accelerating the maturation of dendritic cells into efficient antigen-presenting cells for T-lymphocytes (e.g., GM-CSF, IL-1 and IL-4) (U.S. Pat. No. 5,849,589, incorporated herein by reference in its entirety) and acting as immunoadjuvants (e.g., IL-12, IL-15, IL-23, IL-7, IFN-alpha, IFN-beta).

[00513] CpG immunostimulatory oligonucleotides have also been reported to enhance the effects of adjuvants in a vaccine setting. Without being bound by theory, CpG oligonucleotides act by activating the innate (non-adaptive) immune system via Toll-like receptors (TLR), mainly TLR9. CpG triggered TLR9 activation enhances antigen-specific humoral and cellular responses to a wide variety of antigens, including peptide or protein antigens, live or killed viruses, dendritic cell vaccines, autologous cellular vaccines and polysaccharide conjugates in both prophylactic and therapeutic vaccines. More importantly it enhances dendritic cell maturation and differentiation, resulting in enhanced activation of TH1 cells and strong cytotoxic T-lymphocyte (CTL) generation, even in the absence of CD4 T cell help. The TH1 bias induced by TLR9 stimulation is maintained even in the presence of vaccine adjuvants such as alum or incomplete Freund's adjuvant (IFA) that normally promote a TH2 bias. CpG oligonucleotides show even greater adjuvant activity when formulated or co-administered with other adjuvants or in formulations such as microparticles, nanoparticles, lipid emulsions or similar formulations, which are especially necessary for inducing a strong response when the antigen is relatively weak. They also accelerate the immune response and enable the antigen doses to be reduced by approximately two orders of magnitude, with comparable antibody responses to the full-dose vaccine without CpG in some experiments (Krieg, 2006). US 6,406,705 B1 describes the

combined use of CpG oligonucleotides, non-nucleic acid adjuvants and an antigen to induce an antigen-specific immune response. A CpG TLR9 antagonist is dSLIM (double Stem Loop Immunomodulator) by Mologen (Berlin, Germany). In embodiments dSLIM may be a preferred component of a pharmaceutical composition described herein. Other TLR binding molecules such as RNA binding TLR 7, TLR 8 and/or TLR 9 may also be used.

Methods of Treatment and Preparation

[00514] Engineered T cells and/or engineered natural killer cells may express a membrane-bound IL-15 (e.g., an IL-15/IL-15R α fusion polypeptide) and/or CD8 polypeptide(s) described herein. Further, engineered T cells and/or engineered natural killer cells may express a TCR described herein. The TCR expressed by the engineered T cells and/or engineered natural killer cells may recognize a TAA bound to an HLA as described herein. Engineered T cells and/or engineered natural killer cells of the present disclosure can be used to treat a subject in need of treatment for a condition, for example, a cancer described herein. The cells may be $\alpha\beta$ T cells, $\gamma\delta$ T cells, and/or natural killer cells that express a membrane-bound IL-15 (e.g., an IL-15/IL-15R α fusion polypeptide) and/or a CD8 polypeptide, and optionally a TCR described herein. In embodiments, a CD8 polypeptide may comprise a CD8 α chain and/or a CD8 β chain, and the CD8 α chain and/or CD8 β chain may independently be modified or unmodified.

[00515] A method of treating a condition (e.g., ailment) in a subject with T cells and/or natural killer cells described herein may comprise administering to the subject a therapeutically effective amount of engineered T cells and/or engineered natural killer cells described herein, optionally $\gamma\delta$ T cells. T cells and/or natural killer cells described herein may be administered at various regimens (e.g., timing, concentration, dosage, spacing between treatment, and/or formulation). A subject can also be preconditioned with, for example, chemotherapy, radiation, or a combination of both, prior to receiving engineered T cells and/or engineered natural killer cells of the present disclosure. A population of engineered T cells and/or engineered natural killer cells may also be frozen or cryopreserved prior to being administered to a subject. A population of engineered T cells and/or engineered natural killer cells can include two or more cells that express identical, different, or a combination of identical and different tumor recognition moieties. For instance, a population of engineered T-cells and/or engineered natural killer cells can include several distinct engineered T cells and/or engineered natural killer cells that are designed to recognize different antigens, or different epitopes of the same antigen. The cells may be $\alpha\beta$ T cells, $\gamma\delta$ T cells, and/or natural killer cells that express a membrane-bound IL-15 (e.g., an IL-15/IL-15R α fusion polypeptide) and/or a CD8 polypeptide described herein, and optionally a TCR described herein.

[00516] T cells and/or natural killer cells described herein, including $\alpha\beta$ T-cells and $\gamma\delta$ T cells, may be used to treat various conditions. The cells may be $\alpha\beta$ T cells, $\gamma\delta$ T cells, and/or natural killer cells that express a membrane-bound IL-15 (e.g., an IL-15/IL-15R α fusion polypeptide) and/or a CD8 polypeptide, and optionally a TCR described herein. T cells and/or natural killer cells described herein may be used to treat a cancer, including solid tumors and hematologic malignancies. Non-limiting examples of cancers include: non-small cell lung cancer, small cell lung cancer, melanoma, liver cancer, breast cancer, uterine cancer, Merkel cell carcinoma, pancreatic cancer, gallbladder cancer, bile duct cancer, colorectal cancer, urinary bladder cancer, kidney cancer, leukemia, ovarian cancer, esophageal cancer, brain cancer, gastric cancer, and prostate cancer.

[00517] The T cells and/or natural killer cells described herein may be used to treat an infectious disease. The T cells and/or natural killer cells described herein may be used to treat an infectious disease, an infectious disease may be caused a virus. The T cells and/or natural killer cells described herein may be used to treat an immune disease, such as an autoimmune disease. The cells may be $\alpha\beta$ T cells, $\gamma\delta$ T cells, and/or natural killer cells that express a membrane-bound IL-15 (e.g., an IL-15/IL-15R α fusion polypeptide) and/or a CD8 polypeptide, and optionally a TCR described herein.

[00518] Treatment with T cells and/or natural killer cells described herein, optionally $\gamma\delta$ T cells, may be provided to the subject before, during, and after the clinical onset of the condition. Treatment may be provided to the subject after 1 day, 1 week, 6 months, 12 months, or 2 years after clinical onset of the disease. Treatment may be provided to the subject for more than 1 day, 1 week, 1 month, 6 months, 12 months, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years or more after clinical onset of disease. Treatment may be provided to the subject for less than 1 day, 1 week, 1 month, 6 months, 12 months, or 2 years after clinical onset of the disease. Treatment may also include treating a human in a clinical trial. A treatment can include administering to a subject a pharmaceutical composition comprising engineered T cells described herein. The cells may be $\alpha\beta$ T cells, $\gamma\delta$ T cells, and/or natural killer cells that express a membrane-bound IL-15 (e.g., an IL-15/IL-15R α fusion polypeptide) and/or a CD8 polypeptide, and optionally a TCR described herein.

[00519] In embodiments administration of engineered T cells and/or engineered natural killer cells of the present disclosure to a subject may modulate the activity of endogenous lymphocytes in a subject's body. In embodiments administration of engineered T cells and/or engineered natural killer cells to a subject may provide an antigen to an endogenous T-cell and may boost an immune response. In embodiments the memory T cell may be a CD4⁺ T-cell. In embodiments the memory T cell may be a CD8⁺ T-cell. In embodiments administration of engineered T cells

and/or engineered natural killer cells of the present disclosure to a subject may activate the cytotoxicity of another immune cell. In embodiments the other immune cell may be a CD8⁺ T-cell. In embodiments the other immune cell may be a Natural Killer T-cell. In embodiments administration of engineered $\gamma\delta$ T-cells and/or engineered natural killer cells of the present disclosure to a subject may suppress a regulatory T-cell. In embodiments the regulatory T-cell may be a FOXP3⁺ Treg cell. In embodiments the regulatory T-cell may be a FOXP3⁻ Treg cell. Non-limiting examples of cells whose activity can be modulated by engineered T cells and/or engineered natural killer cells of the disclosure may comprise: hematopoietic stem cells; B cells; CD4; CD8; red blood cells; white blood cells; dendritic cells, including dendritic antigen presenting cells; leukocytes; macrophages; memory B cells; memory T-cells; monocytes; natural killer cells; neutrophil granulocytes; T-helper cells; and T-killer cells. The cells may be $\alpha\beta$ T cells, $\gamma\delta$ T cells, and/or natural killer cells that express a membrane-bound IL-15 (e.g., an IL-15/IL-15R α fusion polypeptide) and/or a CD8 polypeptide, and optionally a TCR described herein. In embodiments, a CD8 polypeptide may comprise a CD8 α chain and/or a CD8 β chain, and the CD8 α chain and/or CD8 β chain may independently be modified or unmodified.

[00520] During most bone marrow transplants, a combination of cyclophosphamide with total body irradiation may be conventionally employed to prevent rejection of the hematopoietic stem cells (HSC) in the transplant by the subject's immune system. In embodiments incubation of donor bone marrow with interleukin-2 (IL-2) ex vivo may be performed to enhance the generation of killer lymphocytes in the donor marrow. Interleukin-2 (IL-2) is a cytokine that may be necessary for the growth, proliferation, and differentiation of wild-type lymphocytes. Current studies of the adoptive transfer of $\gamma\delta$ T-cells into humans may require the co-administration of $\gamma\delta$ T-cells and interleukin-2. However, both low- and high-dosages of IL-2 can have highly toxic side effects. IL-2 toxicity can manifest in multiple organs/systems, most significantly the heart, lungs, kidneys, and central nervous system. In embodiments the disclosure provides a method for administering engineered T cells and/or engineered natural killer cells to a subject without the co-administration of a native cytokine or modified versions thereof, such as IL-2, IL-15, IL-12, IL-21. In embodiments engineered T cells and/or engineered natural killer cells can be administered to a subject without co-administration with IL-2. In embodiments engineered T cells and/or engineered natural killer cells may be administered to a subject during a procedure, such as a bone marrow transplant without the co-administration of IL-2.

[00521] In embodiments the methods may further comprise administering a chemotherapy agent. The dosage of the chemotherapy agent may be sufficient to deplete the patient's T-cell population. The chemotherapy may be administered about 5–7 days prior to administration of T-cells and/or natural killer cells. The chemotherapy agent may be cyclophosphamide, fludarabine,

or a combination thereof. The chemotherapy agent may comprise dosing at about 400–600 mg/m²/day of cyclophosphamide. The chemotherapy agent may comprise dosing at about 10–30 mg/m²/day of fludarabine.

[00522] In embodiments the methods may further comprise pre-treatment of the patient with low-dose radiation prior to administration of the composition comprising T-cells and/or natural killer cells. The low dose radiation may comprise about 1.4 Gy for about 1-6 days, such as about 5 days, prior to administration of the composition comprising T-cells.

[00523] In embodiments the patient may be HLA-A*02.

[00524] In embodiments the patient may be HLA-A*06.

[00525] In embodiments the methods may further comprise administering an anti-PD1 antibody. The anti-PD1 antibody may be a humanized antibody. The anti-PD1 antibody may be pembrolizumab. The dosage of the anti-PD1 antibody may be about 200 mg. The anti-PD1 antibody may be administered every 3 weeks following T-cell administration.

[00526] In embodiments the dosage of T-cells and/or natural killer cells may be between about 0.8–1.2 x 10⁹ T cells and/or natural killer cells. The dosage of the T cells and/or natural killer cells may be about 0.5 x 10⁸ to about 10 x 10⁹ T cells and/or natural killer cells. The dosage of T-cells and/or natural killer cells may be about 1.2–3 x 10⁹ T cells and/or natural killer cells, about 3–6 x 10⁹ T cells and/or natural killer cells, about 10 x 10⁹ T cells and/or natural killer cells, about 5 x 10⁹ T cells and/or natural killer cells, about 0.1 x 10⁹ T cells and/or natural killer cells, about 1 x 10⁸ T cells and/or natural killer cells, about 5 x 10⁸ T cells and/or natural killer cells, about 1.2–6 x 10⁹ T cells and/or natural killer cells, about 1–6 x 10⁹ T cells and/or natural killer cells, or about 1–8 x 10⁹ T cells and/or natural killer cells.

[00527] In embodiments the T cells and/or natural killer cells may be administered in 3 doses. The T-cell and/or natural killer cell doses may escalate with each dose. The T-cells and/or natural killer cells may be administered by intravenous infusion.

[00528] In embodiments the membrane-bound IL-15 and/or CD8 sequences described herein and associated products and compositions may be used autologous or allogenic methods of adoptive cellular therapy. In embodiments, membrane-bound IL-15 sequences, CD8 sequences, T cells and/or natural killer cells thereof, and compositions may be used in, for example, methods described in U.S. Patent Application Publication 2019/0175650; U.S. Patent Application Publication 2019/0216852; U.S. Patent Application Publication 2019/024743; and U.S. Provisional Patent Application 62/980,844, each of which is incorporated by reference in its entirety.

[00529] The disclosure also provides for a population of modified T cells and/or modified natural killer cells that express a membrane-bound IL-15 (e.g., an IL-15/IL-15R α fusion

polypeptide) and/or present an exogenous CD8 polypeptide described herein and/or a T cell receptor wherein the population of modified T cells and/or natural killer cells is activated and expanded with a combination of IL-2 and IL-15. In embodiments, the population of modified T cells and/or natural killer cells is expanded and/or activated with a combination of IL-2, IL-15, and zoledronate. In embodiments, the population of modified T cells and/or natural killer cells is activated with a combination of IL-2, IL-15, and zoledronate while expanded with a combination of IL-2, IL-15, and without zoledronate. The disclosure further provides for use of other interleukins during activation and/or expansion, such as IL-12, IL-18, IL-21, and any combination thereof.

[00530] In an aspect, IL-21, a histone deacetylase inhibitor (HDACi), or any combination thereof may be utilized in the field of cancer treatment, with methods described herein, and/or with ACT processes described herein. In embodiments the present disclosure provides methods for re-programming effector T cells to a central memory phenotype comprising culturing the effector T cells with at least one HDACi together with IL-21. Representative HDACi include, for example, trichostatin A, trapoxin B, phenylbutyrate, valproic acid, vorinostat (suberanilohydroxamic acid), belinostat, panobinostat, dacinostat, entinostat, tacedinaline, and mocetinostat.

[00531] Compositions comprising engineered T cells and/or engineered natural killer cells described herein may be administered for prophylactic and/or therapeutic treatments. In therapeutic applications, pharmaceutical compositions can be administered to a subject already suffering from a disease or condition in an amount sufficient to cure or at least partially arrest the symptoms of the disease or condition. An engineered T-cell and/or engineered natural killer cell can also be administered to lessen a likelihood of developing, contracting, or worsening a condition. Effective amounts of a population of engineered T-cells and/or natural killer cells for therapeutic use can vary based on the severity and course of the disease or condition, previous therapy, the subject's health status, weight, and/or response to the drugs, and/or the judgment of the treating physician. The cells may be $\alpha\beta$ T cells, $\gamma\delta$ T cells, and/or natural killer cells engineered to express a membrane-bound IL-15 (e.g., an IL-15/IL-15R α fusion polypeptide) and/or a CD8 polypeptide described herein and optionally a TCR described herein. In embodiments, a CD8 polypeptide may comprise a CD8 α chain and/or a CD8 β chain, and the CD8 α chain and/or CD8 β chain may independently be modified or unmodified.

Methods of Administration

[00532] One or multiple engineered T cell populations and/or natural killer cell populations described herein may be administered to a subject in any order or simultaneously. If

simultaneously, the multiple engineered T cells and/or engineered natural killer cells can be provided in a single, unified form, such as an intravenous injection, or in multiple forms, for example, as multiple intravenous infusions, subcutaneous injections or pills. Engineered T-cells and/or engineered natural killer cells can be packed together or separately, in a single package or in a plurality of packages. One or all of the engineered T cells and/or engineered natural killer cells can be given in multiple doses. If not simultaneous, the timing between the multiple doses may vary to as much as about a week, a month, two months, three months, four months, five months, six months, or about a year. In embodiments engineered T cells and/or engineered natural killer cells can expand within a subject's body, in vivo, after administration to a subject. Engineered T cells and/or engineered natural killer cells can be frozen to provide cells for multiple treatments with the same cell preparation. Engineered T cells and/or engineered natural killer cells of the present disclosure, and pharmaceutical compositions comprising the same, can be packaged as a kit. A kit may comprise instructions (e.g., written instructions) on the use of engineered T cells and/or engineered natural killer cells and compositions comprising the same.

[00533] A method of treating a cancer may comprise administering to a subject a therapeutically-effective amount of engineered T cells and/or engineered natural killer cells, in which the administration treats the cancer. In embodiments, the therapeutically-effective amount of engineered $\gamma\delta$ T cells and/or engineered natural killer cells may be administered for at least about 10 seconds, about 30 seconds, about 1 minute, about 10 minutes, about 30 minutes, about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 12 hours, about 24 hours, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about 1 week, about 2 weeks, about 3 weeks, about 1 month, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, or about 1 year. In embodiments the therapeutically-effective amount of the engineered T cells and/or engineered natural killer cells may be administered for at least one week. In embodiments the therapeutically-effective amount of engineered T cells and/or engineered natural killer cells may be administered for at least about two weeks.

[00534] Engineered T-cells and/or engineered natural killer cells described herein, optionally $\gamma\delta$ T cells, can be administered before, during, or after the occurrence of a disease or condition, and the timing of administering a pharmaceutical composition comprising an engineered T-cell and/or engineered natural killer cell can vary. For example, engineered T cells and/or engineered natural killer cells can be used as a prophylactic and can be administered continuously to subjects with a propensity to conditions or diseases in order to lessen the likelihood of occurrence of the disease or condition. Engineered T-cells and/or engineered natural killer cells can be administered to a subject during or as soon as possible after the onset of the symptoms.

The administration of engineered T cells and/or engineered natural killer cells can be initiated immediately within the onset of symptoms, within about the first 3 hours of the onset of the symptoms, within about the first 6 hours of the onset of the symptoms, within about the first 24 hours of the onset of the symptoms, within about 48 hours of the onset of the symptoms, or within any period of time from the onset of symptoms. The initial administration can be via any route practical, such as by any route described herein using any formulation described herein. In embodiments the administration of engineered T cells and/or engineered natural killer cells of the present disclosure may be an intravenous administration. One or multiple dosages of engineered T cells and/or engineered natural killer cells can be administered as soon as is practicable after the onset of a cancer, an infectious disease, an immune disease, sepsis, or with a bone marrow transplant, and for a length of time necessary for the treatment of the immune disease, such as, for example, from about 24 hours to about 48 hours, from about 48 hours to about 1 week, from about 1 week to about 2 weeks, from about 2 weeks to about 1 month, from about 1 month to about 3 months. For the treatment of cancer, one or multiple dosages of engineered T cells and/or engineered natural killer cells can be administered years after onset of the cancer and before or after other treatments. In embodiments engineered $\gamma\delta$ T cells and/or engineered natural killer cells can be administered for at least about 10 minutes, about 30 minutes, about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 12 hours, about 24 hours, at least about 48 hours, at least about 72 hours, at least about 96 hours, at least about 1 week, at least about 2 weeks, at least about 3 weeks, at least about 4 weeks, at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about 12 months, at least about 1 year, at least about 2 years at least about 3 years, at least about 4 years, or at least about 5 years. The length of treatment can vary for each subject. The cells may be $\alpha\beta$ T cells, $\gamma\delta$ T cells, and/or natural killer cells that express an IL-15/IL-15R α fusion polypeptide and/or a CD8 polypeptide described herein, optionally a TCR described herein.

[00535] Engineered T-cells and/or engineered natural killer cells expressing a membrane-bound IL-15 (e.g., an IL-15/IL-15R α fusion polypeptide) and/or a CD8 polypeptides described herein, optionally $\alpha\beta$ T cells and/or $\gamma\delta$ T cells, may be present in a composition in an amount of at least about 1×10^3 cells/ml, at least about 2×10^3 cells/ml, at least about 3×10^3 cells/ml, at least about 4×10^3 cells/ml, at least about 5×10^3 cells/ml, at least about 6×10^3 cells/ml, at least about 7×10^3 cells/ml, at least about 8×10^3 cells/ml, at least about 9×10^3 cells/ml, at least about 1×10^4 cells/ml, at least about 2×10^4 cells/ml, at least about 3×10^4 cells/ml, at least about 4×10^4 cells/ml, at least about 5×10^4 cells/ml, at least about 6×10^4 cells/ml, at least about 7×10^4 cells/ml, at least

about 8×10^4 cells/ml, at least about 9×10^4 cells/ml, at least about 1×10^5 cells/ml, at least about 2×10^5 cells/ml, at least about 3×10^5 cells/ml, at least about 4×10^5 cells/ml, at least about 5×10^5 cells/ml, at least about 6×10^5 cells/ml, at least about 7×10^5 cells/ml, at least about 8×10^5 cells/ml, at least about 9×10^5 cells/ml, at least about 1×10^6 cells/ml, at least about 2×10^6 cells/ml, at least about 3×10^6 cells/ml, at least about 4×10^6 cells/ml, at least about 5×10^6 cells/ml, at least about 6×10^6 cells/ml, at least about 7×10^6 cells/ml, at least about 8×10^6 cells/ml, at least about 9×10^6 cells/ml, at least about 1×10^7 cells/ml, at least about 2×10^7 cells/ml, at least about 3×10^7 cells/ml, at least about 4×10^7 cells/ml, at least about 5×10^7 cells/ml, at least about 6×10^7 cells/ml, at least about 7×10^7 cells/ml, at least about 8×10^7 cells/ml, at least about 9×10^7 cells/ml, at least about 1×10^8 cells/ml, at least about 2×10^8 cells/ml, at least about 3×10^8 cells/ml, at least about 4×10^8 cells/ml, at least about 5×10^8 cells/ml, at least about 6×10^8 cells/ml, at least about 7×10^8 cells/ml, at least about 8×10^8 cells/ml, at least about 9×10^8 cells/ml, at least about 1×10^9 cells/ml, or more, from about 1×10^3 cells/ml to about at least about 1×10^8 cells/ml, from about 1×10^5 cells/ml to about at least about 1×10^8 cells/ml, or from about 1×10^6 cells/ml to about at least about 1×10^8 cells/ml.

Uses

[00536] T cells, natural killer (NK) cells, and pharmaceutical compositions described herein may be used in therapy, in particular in a method of treating cancer. The present disclosure therefore also provides the use of the T cells, natural killer (NK) cells, and pharmaceutical compositions described herein in the therapy, in particular in a method of treating cancer. Further, the present disclosure also provides the use of the T cells, natural killer (NK) cells, and pharmaceutical compositions described herein in the manufacture of a medicament, in particular a medicament for the treatment of cancer. The cancer may be selected from the group consisting of non-small cell lung cancer, small cell lung cancer, melanoma, liver cancer, breast cancer, uterine cancer, Merkel cell carcinoma, pancreatic cancer, gallbladder cancer, bile duct cancer, colorectal cancer, urinary bladder cancer, kidney cancer, leukemia, ovarian cancer, esophageal cancer, brain cancer, gastric cancer, and prostate cancer. The features and aspects described in connection with the methods of treating, preparing and administering above are also applicable to the uses described herein, *mutatis mutandis*.

Sequences

[00537] The sequences described herein may comprise about 80%, about 85%, about 90%, about 85%, about 96%, about 97%, about 98%, or about 99%, or about 100% identity to the sequence of any of SEQ ID NO: 1 – 97, 256 – 266, 293, 294, or 305-436. The sequences

described herein may comprise at least about 80%, at least about 85%, at least about 90%, at least about 85%, at least about 96%, at least about 97%, at least about 98%, at least about 99% or 100% identity to the sequence of any of SEQ ID NO: 1 – 97, 256 – 266, or 305-436. A sequence “at least 85% identical to a reference sequence” is a sequence having, on its entire length, 85%, or more, in particular 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with the entire length of the reference sequence.

[00538] In embodiments, the disclosure provides for sequences at least about 80%, at least about 85%, at least about 90%, at least about 85%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identity to WPREmut1 (SEQ ID NO: 256), or WPRE version 2, e.g., WPREmut2 (SEQ ID NO: 257). In another aspect, the disclosure provides for sequences at least 1, 2, 3, 4, 5, 10, 15, or 20 amino acid substitutions in WPREmut1 (SEQ ID NO: 256), or WPRE version 2, e.g., WPREmut2 (SEQ ID NO: 257). In yet another aspect, the disclosure provides for sequences at most 1, 2, 3, 4, 5, 10, 15, or 20 amino acid substitutions in WPREmut1 (SEQ ID NO: 256), or WPRE version 2, e.g., WPREmut2 (SEQ ID NO: 257). In another aspect, the sequence substitutions are conservative substitutions.

[00539] Percentage of identity may be calculated using a global pairwise alignment (e.g., the two sequences are compared over their entire length). Methods for comparing the identity of two or more sequences are well known in the art. The « needle » program, which uses the Needleman-Wunsch global alignment algorithm (Needleman and Wunsch, 1970 J. Mol. Biol. 48:443-453) to find the optimum alignment (including gaps) of two sequences when considering their entire length, may for example be used. The needle program is for example available on the ebi.ac.uk World Wide Web site and is further described in the following publication (*EMBOSS: The European Molecular Biology Open Software Suite* (2000) Rice, P. Longden, I. and Bleasby, A. Trends in Genetics 16, (6) pp. 276—277). The percentage of identity between two polypeptides, in accordance with the present disclosure, is calculated using the EMBOSS: needle (global) program with a “Gap Open” parameter equal to 10.0, a “Gap Extend” parameter equal to 0.5, and a Blosum62 matrix.

[00540] Proteins comprising or consisting of an amino acid sequence “at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical”, “at least about 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical”, or similar recitations, to a reference sequence may comprise mutations such as deletions, insertions and/or substitutions compared to the reference sequence. The reference sequence may be, as non-limiting examples, a wild type sequence, a mature wild type sequence, a native sequence, a truncated wild type sequence, a truncated mature wild type sequence, a truncated native sequence, or a sequence disclosed herein. The reference sequence may be, as non-limiting examples, a wild type sequence, a mature wild type sequence, or a

native sequence. In the case of substitutions, the protein consisting of an amino acid sequence at least or at least about 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a reference sequence may correspond to a homologous sequence derived from another species than the reference sequence.

[00541] Amino acid substitutions may be conservative or non-conservative. In embodiments, substitutions may be conservative substitutions, in which one amino acid is substituted for another amino acid with similar structural and/or chemical properties.

[00542] Conservative substitutions may comprise those, which are described by Dayhoff in “The Atlas of Protein Sequence and Structure. Vol. 5”, Natl. Biomedical Research, the contents of which are incorporated by reference in their entirety. For example, In embodiments amino acids, which belong to one of the following groups, can be exchanged for one another, thus, constituting a conservative exchange: Group 1: alanine (A), proline (P), glycine (G), asparagine (N), serine (S), threonine (T); Group 2: cysteine (C), serine (S), tyrosine (Y), threonine (T); Group 3: valine (V), isoleucine (I), leucine (L), methionine (M), alanine (A), phenylalanine (F); Group 4: lysine (K), arginine (R), histidine (H); Group 5: phenylalanine (F), tyrosine (Y), tryptophan (W), histidine (H); and Group 6: aspartic acid (D), glutamic acid (E). In embodiments a conservative amino acid substitution may be selected from the following of T→A, G→A, A→I, T→V, A→M, T→I, A→V, T→G, and/or T→S.

[00543] A conservative amino acid substitution may comprise the substitution of an amino acid by another amino acid of the same class, for example, (1) nonpolar: Ala, Val, Leu, Ile, Pro, Met, Phe, Trp; (2) uncharged polar: Gly, Ser, Thr, Cys, Tyr, Asn, Gln; (3) acidic: Asp, Glu; and (4) basic: Lys, Arg, His. Other conservative amino acid substitutions may also be made as follows: (1) aromatic: Phe, Tyr, His; (2) proton donor: Asn, Gln, Lys, Arg, His, Trp; and (3) proton acceptor: Glu, Asp, Thr, Ser, Tyr, Asn, Gln (see, for example, U.S. Patent No. 10,106,805, the contents of which are incorporated by reference in their entirety).

[00544] Conservative substitutions may be made in accordance with Table A. Methods for predicting tolerance to protein modification may be found in, for example, Guo et al., Proc. Natl. Acad. Sci., USA, 101(25):9205-9210 (2004), the contents of which are incorporated by reference in their entirety.

Table A: Conservative Amino Acid substitution

Conservative Amino Acid Substitutions	
Amino Acid	Substitutions (others are known in the art)
Ala	Ser, Gly, Cys
Arg	Lys, Gln, His
Asn	Gln, His, Glu, Asp
Asp	Glu, Asn, Gln
Cys	Ser, Met, Thr
Gln	Asn, Lys, Glu, Asp, Arg
Glu	Asp, Asn, Gln
Gly	Pro, Ala, Ser
His	Asn, Gln, Lys
Ile	Leu, Val, Met, Ala
Leu	Ile, Val, Met, Ala
Lys	Arg, Gln, His
Met	Leu, Ile, Val, Ala, Phe
Phe	Met, Leu, Tyr, Trp, His
Ser	Thr, Cys, Ala
Thr	Ser, Val, Ala
Trp	Tyr, Phe
Tyr	Trp, Phe, His
Val	Ile, Leu, Met, Ala, Thr

[00545] The sequences described herein may comprise 1, 2, 3, 4, 5, 10, 15, 20, 25, or 30 amino acid or nucleotide mutations, substitutions, deletions. Any one of SEQ ID NO: 1 – 97, 256 – 266, 293, 294, or 305-436 may comprise 1, 2, 3, 4, 5, 10, 15, 20, 25, or 30 mutations, substitutions, or deletions. In another aspect, any one of SEQ ID NO: 1 – 97, 256 – 266, 293, 294, or 305-436 may comprise at most 1, 2, 3, 4, 5, 10, 15, 20, 25, or 30 mutations, substitutions, or deletions. In an aspect, the mutations or substitutions may be conservative amino acid substitutions.

[00546] Conservative substitutions in the polypeptides described herein may be those shown in Table B under the heading of “conservative substitutions.” If such substitutions result in a change in biological activity, then more substantial changes, denominated “exemplary substitutions” in Table B, may be introduced and the products screened if needed.

Table B: Amino Acid substitution

Amino Acid Substitutions		
Original Residue (naturally occurring amino acid)	Conservative Substitutions	Exemplary Substitutions
Ala (A)	Val	Val; Leu; Ile
Arg (R)	Lys	Lys; Gln; Asn
Asn (N)	Gln	Gln; His; Asp, Lys; Arg
Asp (D)	Glu	Glu; Asn
Cys (C)	Ser	Ser; Ala
Gln (Q)	Asn	Asn; Glu
Glu (E)	Asp	Asp; Gln
Gly (G)	Ala	Ala
His (H)	Arg	Asn; Gln; Lys; Arg
Ile (I)	Leu	Leu; Val; Met; Ala; Phe; Norleucine
Leu (L)	Ile	Norleucine; Ile; Val; Met; Ala; Phe
Lys (K)	Arg	Arg; Gln; Asn
Met (M)	Leu	Leu; Phe; Ile
Phe (F)	Tyr	Leu; Val; Ile; Ala; Tyr
Pro (P)	Ala	Ala
Ser (S)	Thr	Thr
Thr (T)	Ser	Ser
Trp (W)	Tyr	Tyr; Phe
Tyr (Y)	Phe	Trp; Phe; Thr; Ser
Val (V)	Leu	Ile; Leu; Met; Phe; Ala; Norleucine

[00547] Nucleic acids comprising or consisting of a nucleic acid sequence “at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical”, “at least about 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical”, or similar recitations, to a reference sequence may comprise mutations such as deletions, insertions and/or substitutions compared to the reference sequence. The reference sequence may be, as non-limiting examples, a wild type sequence, a mature wild type sequence, a native sequence, a truncated wild type sequence, a truncated mature wild type sequence, a truncated native sequence, or a sequence disclosed herein. The reference sequence may be, as non-limiting examples, a wild type sequence, a mature wild type sequence, or a native sequence. Due, for example, to codon degeneracy, mutations or substitutions to a reference nucleic acid sequence may result in a mutated nucleic acid sequence that encodes protein identical to the protein encoded by the reference sequence. Mutated nucleic acid

sequences that encode a protein having a different sequence from the protein encoded by the reference sequence are also contemplated. Mutated nucleic acid sequences encoding conservative amino acid mutations are contemplated. In the case of substitutions, the nucleic acid sequence at least, or at least about, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a reference sequence may correspond to a homologous sequence derived from another species than the reference sequence.

[00548] Unless otherwise indicated, all terms used herein have the same meaning as they would to one skilled in the art.

[00549] In this specification and the appended claims, the singular forms “a,” “an,” and “the” include plural reference unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which this disclosure belongs.

[00550] It will be understood that each of the elements described above, or two or more together may also find a useful application in other types of methods differing from the type described above. Without further analysis, the foregoing will so fully reveal the gist of the present disclosure that others can, by applying current knowledge, readily adapt it for various applications without omitting features that, from the standpoint of prior art, fairly constitute essential characteristics of the generic or specific embodiments of this disclosure set forth in the appended claims. The foregoing embodiments are presented by way of example only; the scope of the present disclosure is to be limited only by the following claims.

[00551] All references cited in this specification are herein incorporated by reference as though each reference was specifically and individually indicated to be incorporated by reference. The citation of any reference is for its disclosure prior to the filing date and should not be construed as an admission that the present disclosure is not entitled to antedate such reference by virtue of prior invention. Additional information regarding CD8 polypeptides, TCR polypeptides, and further information, may be found in United States Patent Application No. US 17/563,599, filed December 28, 2021, entitled “CD8 POLYPEPTIDES, COMPOSITIONS, AND METHODS OF USING THEREOF”, which is incorporated by reference herein in its entirety.

[00552] Unless otherwise specified herein, ranges of values set forth herein are intended to operate as a scheme for referring to each separate value falling within the range individually, including but not limited to the endpoints of the ranges, and each separate value of each range set forth herein is hereby incorporated into the specification as if it were individually recited.

[00553] This specification may include references to “one embodiment”, “an embodiment”, “embodiments”, “one aspect”, “an aspect”, or “aspects”. Each of these words and phrases is not

intended to convey a different meaning from the other words and phrases. These words and phrases may refer to the same embodiment or aspect, may refer to different embodiments or aspects, and may refer to more than one embodiment or aspect. Various embodiments and aspects may be combined in any manner consistent with this disclosure.

[00554] “Activation” as used herein refers broadly to the state of a T cell that has been sufficiently stimulated to induce detectable cellular proliferation. Activation can also be associated with induced cytokine production, and detectable effector functions. The term “activated T cells” refers to, among other things, T cells that are proliferating.

[00555] “Antibodies” as used herein refer broadly to antibodies or immunoglobulins of any isotype, fragments of antibodies, which retain specific binding to antigen, including, but not limited to, Fab, Fab', Fab'-SH, (Fab')₂ Fv, scFv, divalent scFv, and Fd fragments, chimeric antibodies, humanized antibodies, single-chain antibodies, and fusion proteins including an antigen-specific targeting region of an antibody and a non-antibody protein. Antibodies are organized into five classes—IgG, IgE, IgA, IgD, and IgM.

[00556] “Antigen” or “Antigenic,” as used herein, refers broadly to a peptide or a portion of a peptide capable of being bound by an antibody which is additionally capable of inducing an animal to produce an antibody capable of binding to an epitope of that antigen. An antigen may have one epitope or have more than one epitope. The specific reaction referred to herein indicates that the antigen will react, in a highly selective manner, with its corresponding antibody and not with the multitude of other antibodies which may be evoked by other antigens.

[00557] “Chimeric antigen receptor” or “CAR” or “CARs” as used herein refers broadly to genetically modified receptors, which graft an antigen specificity onto cells, for example T cells, NK cells, macrophages, and stem cells. CARs can include at least one antigen-specific targeting region (ASTR), a hinge or stalk domain, a transmembrane domain (TM), one or more co-stimulatory domains (CSDs), and an intracellular activating domain (IAD). In certain embodiments, the CSD is optional. In embodiments, the CAR is a bispecific CAR, which is specific to two different antigens or epitopes. After the ASTR binds specifically to a target antigen, the IAD activates intracellular signaling. For example, the IAD can redirect T cell specificity and reactivity toward a selected target in a non-MHC-restricted manner, exploiting the antigen-binding properties of antibodies. The non-MHC-restricted antigen recognition gives T cells expressing the CAR the ability to recognize an antigen independent of antigen processing, thus bypassing a major mechanism of tumor escape. Moreover, when expressed in T cells, CARs advantageously do not dimerize with endogenous T cell receptor (TCR) alpha and beta chains.

[00558] “Cytotoxic T lymphocyte” (CTL) as used herein refers broadly to a T lymphocyte that expresses CD8 on the surface thereof (*e.g.*, a CD8⁺ T cell). Such cells may be “memory” T cells (T_M cells) that are antigen-experienced.

[00559] “Effective amount”, “therapeutically effective amount”, or “efficacious amount” as used herein refers broadly to the amount of an agent, or combined amounts of two agents, that, when administered to a mammal or other subject for treating a disease, is sufficient to affect such treatment for the disease. The “therapeutically effective amount” will vary depending on the agent(s), the disease and its severity and the age, weight, etc., of the subject to be treated.

[00560] “Genetically modified” as used herein refers broadly to methods to introduce exogenous nucleic acids into a cell, whether or not the exogenous nucleic acids are integrated into the genome of the cell. “Genetically modified cell” as used herein refers broadly to cells that contain exogenous nucleic acids whether or not the exogenous nucleic acids are integrated into the genome of the cell.

[00561] “Immune cells” as used herein refers broadly to white blood cells (leukocytes) derived from hematopoietic stem cells (HSC) produced in the bone marrow “Immune cells” include, without limitation, lymphocytes (T cells, B cells, natural killer (NK) (CD3-CD56⁺) cells) and myeloid-derived cells (neutrophil, eosinophil, basophil, monocyte, macrophage, dendritic cells). “T cells” include all types of immune cells expressing CD3 including T-helper cells (CD4⁺ cells), cytotoxic T-cells (CD8⁺ cells), T-regulatory cells (Treg) and gamma-delta T cells, and NK T cells (CD3⁺ and CD56⁺). A skilled artisan will understand T cells and/or NK cells, as used throughout the disclosure, can include only T cells, only NK cells, or both T cells and NK cells. In certain illustrative embodiments and aspects provided herein, T cells are activated and transduced. Furthermore, T cells are provided in certain illustrative composition embodiments and aspects provided herein. A “cytotoxic cell” includes CD8⁺ T cells, natural-killer (NK) cells, NK-T cells, $\gamma\delta$ T cells, and neutrophils, which are cells capable of mediating cytotoxicity responses.

[00562] “Individual,” “subject,” “host,” and “patient,” as used interchangeably herein, refer broadly to a mammal, including, but not limited to, humans, murines (*e.g.*, rats, mice), lagomorphs (*e.g.*, rabbits), non-human primates, canines, felines, and ungulates (*e.g.*, equines, bovines, ovines, porcines, caprines).

[00563] “Peripheral blood mononuclear cells” or “PBMCs” as used herein refers broadly to any peripheral blood cell having a round nucleus. PBMCs include lymphocytes, such as T cells, B cells, and NK cells, and monocytes.

[00564] “Polynucleotide” and “nucleic acid”, as used interchangeably herein, refer broadly to a polymeric form of nucleotides of any length, either ribonucleotides or deoxyribonucleotides.

Thus, this term includes, but is not limited to, single-, double-, or multi-stranded DNA or RNA, genomic DNA, cDNA, DNA-RNA hybrids, or a polymer including purine and pyrimidine bases or other natural, chemically or biochemically modified, non-natural, or derivatized nucleotide bases.

[00565] “T cell” or “T lymphocyte,” as used herein, refer broadly to thymocytes, naïve T lymphocytes, immature T lymphocytes, mature T lymphocytes, resting T lymphocytes, or activated T lymphocytes. Illustrative populations of T cells suitable for use in particular embodiments include, but are not limited to, helper T cells (HTL; CD4⁺ T cell), a cytotoxic T cell (CTL; CD8⁺ T cell), CD4⁺CD8⁺ T cell, CD4⁺CD8[−] T cell, natural killer T cell, T cells expressing $\alpha\beta$ TCR ($\alpha\beta$ T cells), T cells expressing $\gamma\delta$ TCR ($\gamma\delta$ T cells), or any other subset of T cells. Other illustrative populations of T cells suitable for use in particular embodiments include, but are not limited to, T cells expressing one or more of the following markers: CD3, CD4, CD8, CD27, CD28, CD45RA, CD45RO, CD62L, CD127, CD197, and HLA-DR and if desired, can be further isolated by positive or negative selection techniques.

[00566] In the present disclosure, the term “homologous” refers to the degree of identity between sequences of two amino acid sequences, *e.g.*, peptide or polypeptide sequences. The aforementioned “homology” is determined by comparing two sequences aligned under optimal conditions over the sequences to be compared. Such a sequence homology can be calculated by creating an alignment using, for example, the ClustalW algorithm. Commonly available sequence analysis software, more specifically, Vector NTI, GENETYX or other tools are provided by public databases.

[00567] The terms “sequence homology” or “sequence identity” are used interchangeably herein. For the purpose of this disclosure, in order to determine the percentage of sequence homology or sequence identity of two amino acid sequences or of two nucleotide sequences, the sequences are aligned for optimal comparison purposes. In order to optimize the alignment between the two sequences, gaps may be introduced in any of the two sequences that are compared. Such alignment can be carried out over the full-length of the sequences being compared. Alternatively, the alignment may be carried out over a shorter length, for example over about 5, about 10, about 20, about 50, about 100 or more nucleotides or amino acids. The sequence identity is the percentage of identical matches between the two sequences over the reported aligned region.

[00568] A comparison of sequences and determination of percentage of sequence identity between two sequences can be accomplished using a mathematical algorithm. The skilled person will be aware of the fact that several different computer programs are available to align two sequences and determine the identity between two sequences (Kruskal, J. B. (1983) An overview

of sequence comparison. In D. Sankoff and J. B. Kruskal, (ed.), Time warps, string edits and macromolecules: the theory and practice of sequence comparison, Addison Wesley). The percent sequence identity between two amino acid sequences or between two nucleotide sequences may be determined using the Needleman and Wunsch algorithm for the alignment of two sequences. (Needleman, S. B. and Wunsch, C. D. (1970) J. Mol. Biol. 48, 443-453). Both amino acid sequences and nucleotide sequences can be aligned by the algorithm. The Needleman-Wunsch algorithm has been implemented in the computer program NEEDLE. For the purpose of this disclosure, the NEEDLE program from the EMBOSS package was used (version 2.8.0 or higher, EMBOSS: The European Molecular Biology Open Software Suite (2000) Rice, Longden, and Bleasby, Trends in Genetics 16, (6) 276-277, emboss.bioinformatics.nl/). For amino acid sequences, EBLOSUM62 is used for the substitution matrix. For nucleotide sequence, EDNAFULL is used. The optional parameters used are a gap-open penalty of 10 and a gap extension penalty of 0.5. The skilled person will appreciate that all these different parameters will yield slightly different results but that the overall percentage identity of two sequences is not significantly altered when using different algorithms.

[00569] After alignment by the program NEEDLE as described above the percentage of sequence identity between a query sequence and a sequence of the present disclosure is calculated as follows: Number of corresponding positions in the alignment showing an identical amino acid or identical nucleotide in both sequences divided by the total length of the alignment after subtraction of the total number of gaps in the alignment. The identity can be obtained from NEEDLE by using the NOBRIEF option and is labelled in the output of the program as "longest-identity". The nucleotide and amino acid sequences of the present disclosure can further be used as a "query sequence" to perform a search against sequence databases to, for example, identify other family members or related sequences. Such searches can be performed using the NBLAST and XBLAST programs (version 2.0) of Altschul *et al.* (1990) J. Mol. Biol. 215:403-10. BLAST nucleotide searches can be performed with the NBLAST program, score= 100, word length= 12 to obtain nucleotide sequences homologous to polynucleotides of the present disclosure. BLAST protein searches can be performed with the XBLAST program, score= 50, word length= 3 to obtain amino acid sequences homologous to polypeptides of the present disclosure. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul *et al.* (1997) Nucleic Acids Res. 25(17): 3389-3402. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (*e.g.*, XBLAST and NBLAST) can be used.

[00570] "T-cell receptor (TCR)" as used herein refers broadly to a protein receptor on T cells that is composed of a heterodimer of an alpha (α) and beta (β) chain, although in some cells the

TCR consists of gamma and delta (γ/δ) chains. The TCR may be modified on any cell comprising a TCR, including a helper T cell, a cytotoxic T cell, a memory T cell, regulatory T cell, natural killer T cell, or a gamma delta T cell.

[00571] The TCR is generally found on the surface of T lymphocytes (or T cells) that is generally responsible for recognizing antigens bound to major histocompatibility complex (MHC) molecules. It is a heterodimer consisting of an alpha and beta chain in 95% of T cells, while 5% of T cells have TCRs consisting of gamma and delta chains. Engagement of the TCR with antigen and MHC results in activation of its T lymphocyte through a series of biochemical events mediated by associated enzymes, co-receptors, and specialized accessory molecules. In immunology, the CD3 antigen (CD stands for cluster of differentiation) is a protein complex composed of four distinct chains (CD3- γ , CD3 δ , and two times CD3 ϵ) in mammals, that associate with molecules known as the T-cell receptor (TCR) and the ζ -chain to generate an activation signal in T lymphocytes. The TCR, ζ -chain, and CD3 molecules together comprise the TCR complex. The CD3- γ , CD3 δ , and CD3 ϵ chains are highly related cell surface proteins of the immunoglobulin superfamily containing a single extracellular immunoglobulin domain. The transmembrane region of the CD3 chains is negatively charged, a characteristic that allows these chains to associate with the positively charged TCR chains (TCR α and TCR β). The intracellular tails of the CD3 molecules contain a single conserved motif known as an immunoreceptor tyrosine-based activation motif or ITAM for short, which is essential for the signaling capacity of the TCR.

[00572] “Treatment,” “treating,” and the like, as used herein refer broadly to obtaining a desired pharmacologic and/or physiologic effect. The effect may be prophylactic in terms of completely or partially preventing a disease or symptom thereof and/or may be therapeutic in terms of a partial or complete cure for a disease and/or adverse effect attributable to the disease. “Treatment,” as used herein, covers any treatment of a disease in a mammal, *e.g.*, in a human, and includes: (a) preventing the disease from occurring in a subject which may be predisposed to the disease but has not yet been diagnosed as having it; (b) inhibiting the disease, *e.g.*, arresting its development; and (c) relieving the disease, *e.g.*, causing regression of the disease.

[00573] The ability of dendritic cells (DC) to activate and expand antigen-specific CD8⁺ T cells may depend on the DC maturation stage and that DCs may need to receive a “licensing” signal, associated with IL-12 production, in order to elicit cytolytic immune response. In particular, the provision of signals through CD40 Ligand (CD40L)-CD40 interactions on CD4⁺ T cells and DCs, respectively, may be considered important for the DC licensing and induction of cytotoxic CD8⁺ T cells. DC licensing may result in the upregulation of co-stimulatory molecules, increased survival and better cross-presenting capabilities of DCs. This process may

be mediated via CD40/CD40L interaction [S. R. Bennet et al., "Help for cytotoxic T-cell responses is mediated by CD40 signalling," Nature 393(6684):478-480 (1998); S. P. Schoenberger et al., "T-cell help for cytotoxic T-cell help is mediated by CD40-CD40L interactions," Nature 393(6684):480-483 (1998)], but CD40/CD40L-independent mechanisms also exist (CD70, LT β R). In addition, a direct interaction between CD40L expressed on DCs and CD40 on expressed on CD8⁺ T-cells has also been suggested, providing a possible explanation for the generation of helper-independent CTL responses [S. Johnson et al., "Selected Toll-like receptor ligands and viruses promote helper-independent cytotoxic T-cell priming by upregulating CD40L on dendritic cells," Immunity 30(2):218-227 (2009)].

EXAMPLE 1

Exemplary Nucleic Acid and Amino Acid Sequences

Table 2A: CD8-TCR Constructs

Construct #	Nucleic Acid (SEQ ID NO)	Amino Acid (SEQ ID NO)
1	295	296
2	297	298
8	299	300
9	287	288
9b	287	288
10	291	292
10n	291	292
11	285	286
11n	285	286
12	301	302
13	267	268
14	269	270
15	271	272
16	273	274
17	275	276
18	277	278
19	279	280
21	281	282

Construct #	Nucleic Acid (SEQ ID NO)	Amino Acid (SEQ ID NO)
22	283	284
25	289	290

Table 2B: mbIL-15 Constructs

Construct	IL-15-L-IL-15R α Nucleic Acid (SEQ ID NO)	IL-15-L-IL-15R α Amino Acid (SEQ ID NO)	IgESP-IL-15-L-IL-15R α Nucleic Acid (SEQ ID NO)	IgESP-IL-15-L-IL-15R α Amino Acid (SEQ ID NO)	IgESP-IL-15-L-IL-15R α -WPRE Nucleic Acid (SEQ ID NO)
A/A'	318	317	338	337	357
B/B'	320	319	340	339	358
C/C'	322	321	342	341	359
D/D'	324	323	344	343	360
E/E'	326	325	346	345	361
F/F'	328	327	348	347	362
G/G'	330	329	350	349	363
H/H'	332	331	352	351	364
I/I'	334	333	354	353	365
J/J'	336	335	356	355	366

“IgESP” refers to a signal protein derived from IgE.

Table 2C: IL-15 Sequences

Amino Acid (SEQ ID NO)	Nucleotide (SEQ ID NO)
305	436
307	308

Table 2D: IL-15R α Sequences

Amino Acid (SEQ ID NO)	Nucleotide (SEQ ID NO)
309	310
311	312

313	314
315	316

[00574] The inventors found that the various CD8 elements in the vector lead to a surprising increase in expression and activity. For example, despite the observation that Construct #10 has lower viral titers than Constructs #9b, #11, and #12 (FIG. 5A), T cells transduced with Construct #10 expressing CD8 $\alpha\beta$ heterodimer and TCR at the lowest viral volumetric concentration, e.g., 1.25 μ l/10⁶ cells, generated higher CD8+CD4+TCR+ cells (56.7%, FIG. 9B) than that of transduced with Construct #9b expressing CD8 α and TCR (42.3%, FIG. 9A), Construct #11 expressing CD8 α CD8 β stalk with CD8 α transmembrane and intracellular domain and TCR (51.6%, FIG. 9C), and Construct #12 expressing CD8 α CD8 β stalk with Neural Cell Adhesion Molecule 1 (NCAM1) transmembrane and intracellular domain and TCR (14.9%, FIG. 9D).

[00575] A vector may comprise any one or more of nucleic acid sequences of SEQ ID NO: 72, 73, 267, 269, 271, 273, 275, 277, 279, 281, 283, 285, 287, 289, 291, 295, 297, 299, 301, 318, 320, 322, 324, 326, 328, 330, 332, 334, 336, 338, 340, 342, 344, 346, 348, 350, 352, 354, 356-366, 433-436, or SEQ ID NO: 308 directly or indirectly fused to the 5' end of SEQ ID NO: 310 with or without a nucleic acid encoding a linker therebetween; SEQ ID NO: 308 directly or indirectly fused to the 5' end of SEQ ID NO: 312 with or without a nucleic acid encoding a linker therebetween; SEQ ID NO: 308 directly or indirectly fused to the 5' end of SEQ ID NO: 314 with or without a nucleic acid encoding a linker therebetween; or SEQ ID NO: 308 directly or indirectly fused to the 5' end of 316 with or without a nucleic acid encoding a linker therebetween. A linker may be as described herein. Optionally SEQ ID NO: 368 may be directly or indirectly fused to a 5' end of SEQ ID NO: 308.

[00576] A T-cell and/or natural killer cell or any combination thereof may be transduced to express any one or more of the nucleic acid of SEQ ID NO: 72, 73, 267, 269, 271, 273, 275, 277, 279, 281, 283, 285, 287, 289, 291, 295, 297, 299, 301, 318, 320, 322, 324, 326, 328, 330, 332, 334, 336, 338, 340, 342, 344, 346, 348, 350, 352, 354, 356-366, or 433-436; or SEQ ID NO: 308 directly or indirectly fused to the 5' end of SEQ ID NO: 310 with or without a nucleic acid encoding a linker therebetween; SEQ ID NO: 308 directly or indirectly fused to the 5' end of SEQ ID NO: 312 with or without a nucleic acid encoding a linker therebetween; SEQ ID NO: 308 directly or indirectly fused to the 5' end of SEQ ID NO: 314 with or without a nucleic acid encoding a linker therebetween; or SEQ ID NO: 308 directly or indirectly fused to the 5' end of SEQ ID NO: 316 with or without a nucleic acid encoding a linker therebetween. A linker may be as described herein. Optionally SEQ ID NO: 368 may be directly or indirectly fused to a 5' end of SEQ ID NO: 308.

[00577] A vector may comprise any one or more of nucleic acid sequences of SEQ ID NO: 72, 72, 267, 269, 271, 273, 275, 277, 279, 281, 283, 285, 287, 289, 291, 295, 297, 299, 301, 318, 320, 322, 324, 326, 328, 330, 332, 334, 338, 340, 342, 344, 346, 348, 350, 352, 354, 357-365, or 433-436; or SEQ ID NO: 308 directly or indirectly fused to the 5' end of SEQ ID NO: 312 with or without a nucleic acid encoding a linker therebetween; SEQ ID NO: 308 directly or indirectly fused to the 5' end of SEQ ID NO: 314 with or without a nucleic acid encoding a linker therebetween; or SEQ ID NO: 308 directly or indirectly fused to the 5' end of SEQ ID NO: 316 with or without a nucleic acid encoding a linker therebetween. A linker may be as described herein. Optionally SEQ ID NO: 368 may be directly or indirectly fused to a 5' end of SEQ ID NO: 308.

[00578] A T-cell and/or natural killer cell or any combination thereof may be transduced to express any one or more of the nucleic acid of SEQ ID NO: 72, 73, 267, 269, 271, 273, 275, 277, 279, 281, 283, 285, 287, 289, 291, 295, 297, 299, 301, 318, 320, 322, 324, 326, 328, 330, 332, 334, 338, 340, 342, 344, 346, 348, 350, 352, 354, 357-365, or 433-436, or SEQ ID NO: 308 directly or indirectly fused to the 5' end of SEQ ID NO: 312 with or without a nucleic acid encoding a linker therebetween; SEQ ID NO: 308 directly or indirectly fused to the 5' end of SEQ ID NO: 314 with or without a nucleic acid encoding a linker therebetween; or SEQ ID NO: 308 directly or indirectly fused to the 5' end of SEQ ID NO: 316 with or without a nucleic acid encoding a linker therebetween. A linker may be as described herein. Optionally SEQ ID NO: 368 may be directly or indirectly fused to the 5' end of SEQ ID NO: 308.

Table 2E: CD8 β α .TCR.mbIL15. Constructs

Construct #	Nucleotide (SEQ ID NO)
26	438
27	439
28	440
29	441
30	442
31	443
32	444
33	445
34	446
35	447

[00579] A vector may comprise any one or more of nucleic acid sequences of SEQ ID NO: 72, 73, 267, 269, 271, 273, 275, 277, 279, 281, 283, 285, 287, 289, 291, 295, 297, 299, 301, 318, 322, 326, 328, 330, 332, 334, 338, 342, 346, 348, 350, 352, 354, 357, 359, 361-365, 433-436, or 438 to 447.

[00580] A T-cell and/or natural killer cell or any combination thereof may be transduced to express any one or more of the nucleic acid of SEQ ID NO: 72, 73, 267, 269, 271, 273, 275, 277, 279, 281, 283, 285, 287, 289, 291, 295, 297, 299, 301, 318, 322, 326, 328, 330, 332, 334, 338, 342, 346, 348, 350, 352, 354, 357, 359, 361-365, or 433-436.

[00581] A membrane-bound IL-15 may comprise an IL-15 amino acid sequence selected from Table 2C linked directly or indirectly to an IL-15R α amino acid sequence selected from Table 2D. A membrane-bound IL-15 may be encoded by an IL-15 nucleic acid sequence selected from Table 2C linked directly or indirectly to an IL-15R α nucleic acid sequence selected from Table 2D. A signal peptide may be operatively coupled to the IL-15 or IL-15R α . The signal peptide may be derived from an IgE. A signal peptide derived from IgE may comprise SEQ ID NO: 367 and/or may be encoded by SEQ ID NO: 368.

[00582] However, In embodiments nucleic acids, vectors, and/or T cells and/or natural killer cells do not comprise and/or are not transduced to express (i) SEQ ID NO: 336, 356, or 366, (ii) any sequence having about 80%, about 85%, about 90%, or about 95% or more sequence identity to SEQ ID NO: 336, 356, or 366, (iii) SEQ ID NO: 308 directly or indirectly fused to the 5' end of SEQ ID NO: 310 with a nucleic acid encoding a linker therebetween; or (iv) any sequence having about 80%, about 85%, about 90%, or about 95% or more sequence identity to SEQ ID NO: 308 directly or indirectly fused to the 5' end of SEQ ID NO: 310 with a nucleic acid sequence encoding a linker therebetween.

[00583] Several of the elements of the constructs in Table 2 are described in Table 3.

Table 3. Representative Protein and Nucleic Acid (DNA) Sequences

SEQ ID NO:	Description	Sequence
1	CD8 α Ig-like domain-1	SQFRVSPLDRTWNLGETVELKCQVLLSNPTSGCSWLFQP RGAAASPTFLLYLSQNKPKAAEGLDTQRFS GKRLGDTF VLTLSDFRRENEGYFCSALSNSIMYFSHFVPVFLPA
2	CD8 β stalk region	SVVDLPTTAQPTKKSTLKKRVCRLRPETQKGPLCSP

3	CD8 α transmembrane domain	IYIWAPLAGTCGVLLLSLVIT
4	CD8 α cytoplasmic tail	LYCNHRNRRRVCKCPRPVVKSGDKPSLSARYV
5	m1CD8 α (signal- less)	SQFRVSPLDRTWNLGETVELKCQVLLSNPTSGCSWLFQPRGAAASPTFLLYLSQNKPKAAEGLDTQRFSGKRLGDTFVLTLSDFRRENEGYYFCSALSNSIMYFSHFVPVFLPASVVDLPTTAQPTKKSTLKKRVCRLRPETQKGPLCSPIYIWA PLAGTCGVLLLSLVITLYCNHRNRRRVCKCPRPVVKSGDKPSLSARYV
6	CD8 α Signal peptide	MALPVTALLPLALLHAARP
7	m1CD8 α	MALPVTALLPLALLHAARPSQFRVSPLDRTWNLGETVELKCQVLLSNPTSGCSWLFQPRGAAASPTFLLYLSQNKPKAAEGLDTQRFSGKRLGDTFVLTLSDFRRENEGYYFCSALSNSIMYFSHFVPVFLPASVVDLPTTAQPTKKSTLKKRVCRLRPETQKGPLCSPIYIWA PLAGTCGVLLLSLVITLYCNHRNRRRVCKCPRPVVKSGDKPSLSARYV
8	CD8 β 1	MRPRLWLLAAQLTVLHGNSVLQQTPAYIKVQTNKMLMSCEAKISLSNMRIYWLRQRQAPSSDSHHEFLALWDS AKGTIHGEEVEQEKIAVFRDASRFILNLTSVKPEDSGIYFCMIVGSPELTFGKGTQLSVVDLPTTAQPTKKSTLKKRVCRLRPETQKGPLCSPIITLGLLVAGVLVLLVSLGVAIHLC CRRRRARLRFMKQPQGEGISGTFVPQCLHGYYSNNTTSQKLLNPWILKT
9	CD8 β 2	MRPRLWLLAAQLTVLHGNSVLQQTPAYIKVQTNKMLMSCEAKISLSNMRIYWLRQRQAPSSDSHHEFLALWDS AKGTIHGEEVEQEKIAVFRDASRFILNLTSVKPEDSGIYFCMIVGSPELTFGKGTQLSVVDLPTTAQPTKKSTLKKRVCRLRPETQKGLKGVYQEPLSPNACMDTTAILQPHRSC LTHGS
10	CD8 β 3	LQQTPAYIKVQTNKMLMSCEAKISLSNMRIYWLRQRQAPSSDSHHEFLALWDS AKGTIHGEEVEQEKIAVFRDASR

		FILNLTSVKPEDSGIYFCMIVGSPELTFGKGTQLSVVDFLP TTAQPTKKSTLKKRVCRLPRPETQKGPLCSPITLGLLVAG VLVLLVSLGVAIHLCCRRRRARLRFMKQFYK
11	CD8 β 4	LQQTPAYIKVQTNKMVMLSCEAKISLSNMRIYWLRQRQ APSSDSHHEFLALWDSAKGTIHGEEVEQEKIAVFRDASR FILNLTSVKPEDSGIYFCMIVGSPELTFGKGTQLSVVDFLP TTAQPTKKSTLKKRVCRLPRPETQKGPLCSPITLGLLVAG VLVLLVSLGVAIHLCCRRRRARLRFMKQLRLHPLEKCSR MDY
12	CD8 β 5	LQQTPAYIKVQTNKMVMLSCEAKISLSNMRIYWLRQRQ APSSDSHHEFLALWDSAKGTIHGEEVEQEKIAVFRDASR FILNLTSVKPEDSGIYFCMIVGSPELTFGKGTQLSVVDFLP TTAQPTKKSTLKKRVCRLPRPETQKGPLCSPITLGLLVAG VLVLLVSLGVAIHLCCRRRRARLRFMKQKFNIVCLKISG FTTCCCFQILQISREYGFVLLQKDIGQ
13	CD8 β 6	LQQTPAYIKVQTNKMVMLSCEAKISLSNMRIYWLRQRQ APSSDSHHEFLALWDSAKGTIHGEEVEQEKIAVFRDASR FILNLTSVKPEDSGIYFCMIVGSPELTFGKGTQLSVVDFLP TTAQPTKKSTLKKRVCRLPRPETQKGPLCSPITLGLLVAG VLVLLVSLGVAIHLCCRRRRARLRFMKQKFNIVCLKISG FTTCCCFQILQISREYGFVLLQKDIGQ
14	CD8 β 7	LQQTPAYIKVQTNKMVMLSCEAKISLSNMRIYWLRQRQ APSSDSHHEFLALWDSAKGTIHGEEVEQEKIAVFRDASR FILNLTSVKPEDSGIYFCMIVGSPELTFGKGTQLSVVDFLP TTAQPTKKSTLKKRVCRLPRPETQKGPLCSPITLGLLVAG VLVLLVSLGVAIHLCCRRRRARLRFMKQPQGEGISGTFV PQCLHGYYSNTTTSQKLLNPWILKT
15	R11KEA alpha chain	MEKNPLAAPLLILWFHLDVSSILNVEQSPQSLHVQEGD STNFTCSFPSSNFYALHWYRKETAKSPEALFVMTLNGDE KKKGRISATLNTKEGYSYLYIKGSQPEDSATYLCALYNN NDMRFGAGRTLTVKPNIQNPDPVYQLRDSKSSDKSVC LFTDFDSQTNVSQSKSDVYITDKTVLDMRSMDFKSNS AVAWSNKSDFACANAFNNSIIPEDTFFPSPESSCDVKLVE KSFETDTNLFQNLVIGFRILLKLVAGFNLLMTLRLWSS

16	R11KEA beta chain	MDSWTFCCVSLCILVAKHTDAGVIQSPRHEVTEMGQEV TLRCKPISGHNSLFWYRETMMRGLELLIYFNNNPIDDS GMPEDRFS AKMPNASFSTLKIQPSEPRDSAVYFCASSPGS TDTQYFGPGTRLTVLEDLKNVFPPEVAVFEPSEAEISHTQ KATLVCLATGFYDPDHVELSWWVNGKEVHSGVSTDPQP LKEQPALNDSRYCLSSRLRVSATFWQNPRNHFRCQVQF YGLSENDEWTQDRAKPVTQIVSAEAWGRADCGFTSESY QQGVLSATILYEILLGKATLYAVLV SALVLMAMVKRKD SRG
17	R20P1H7 alpha chain	MEKMLECAFIVLWLQLGWLSGEDQVTQSPEALRLQEGE SSSLNCSYTVSGLRGLFWYRQDPGKGPEFLFTLYSAGEE KEKERLKATLTKKESFLHITAPKPEDSATYLC AVQGENS GYSTLTFGKGTMMLVSPDIQNPDPAVYQLRDSKSSDKSV CLFTDFDSQTNVSQSKSDSVYITDKTVLDMRSMDFKSN SAVAWSNKSDFACANAFNNSIIPEDTFFPSPESSCDVKLV EKSFETDTNLFQNL SVIGFRILLK VAGFNLLMTLRLW SS
18	R20P1H7 beta chain	MGPQLLGYVVLCLLGAGPLEAQVTQNPRYLITVTGKKL TVTCSQNMNHEYMSWYRQDPGLGLRQIYYSMNVEVTD KGDVPEGYKVS RKEKRNFLILESPSPNQTSLYFCASSLG PGLAAYNEQFFGPGTRLTVLEDLKNVFPPEVAVFEPSEA EISHTQKATLVCLATGFYDPDHVELSWWVNGKEVHSGVS TDPQPLKEQPALNDSRYCLSSRLRVSATFWQNPRNHFRC QVQFYGLSENDEWTQDRAKPVTQIVSAEAWGRADCGF TSESYQQGVLSATILYEILLGKATLYAVLV SALVLMAMV KRKDSRG
19	R7P1D5 alpha chain	MKTFAGFSFLFLWLQLDCMSRGEDVEQSLFLSVREGDSS VINCTYTDSSSTYLWYKQEPGAGLQLLTYIFSNMDMK QDQRLTVLLNKKDKHLSLRIADTQTGDSAIYFCAEYSSA SKIIFGSGTRL SIRPNIQNPDPAVYQLRDSKSSDKSVCLFT DFDSQTNVSQSKSDSVYITDKTVLDMRSMDFKSN SAVA WSNKSDFACANAFNNSIIPEDTFFPSPESSCDVKLV EKSF ETDTNLFQNL SVIGFRILLK VAGFNLLMTLRLWSS

20	R7P1D5 beta chain	MGSWTLCCVSLCILVAKHTDAGVIQSPRHEVTEMGQEV TLRCKPISGHDYLFWYRQTM MRGLELLIYFNNNPIDDS GMPEDRFS AKMPNASFSTLKIQPSEPRDS AVYFCASRAN TGELFFGEGSRLTVLEDLKNVFPPEVAVFEPSEAEISHTQ KATLVCLATGFYDPDHVELSWWVNGKEVHSGVSTDPQP LKEQPALNDSRYCLSSRLRVSATFWQNPRNHFRCQVQF YGLSENDEWTQDRAKPVTQIVSAEAWGRADCGFTSESY QQGVLSATILYEILLGKATLYAVLVSALVLMAMVKRKD SRG
21	R10P2G12 alpha chain	MLTASLLRAVIASICVVSSMAQKVTQAQTEISVVEKEDV TLDCVYETRDTTYLFWYKQPPSGELVFLIRNSFDEQN EISGRYSWNFQKSTSSFNFTITASQVVDS AVYFCALSEGN SGNTPLVFGKGTRLSVIANIQNPDP AVYQLRDSKSSDKS VCLFTDFDSQTNVSQSKDSDVYITDKTVLDMRSMDFKS NSAVAWSNKSDFACANAFNNSIIPEDTFFPSPESSCDVKL VEKSFETDTNLFQNL SVIGFRILLK VAGFNLLMTLRL WSS
22	R10P2G12 beta chain	MGIRLLCRVAFCFLAVGLVDVKVTQSSRYLVKRTGEKV FLECVQMDHENMFWYRQDPGLGLRLIYFSYDVKMKE KGDIEGYSVSREKKERFSLILESASTNQTSMYLCASSLS SGSHQETQYFGPGTRLLVLEDLKNVFPPEVAVFEPSEAEI SHTQKATLVCLATGFYDPDHVELSWWVNGKEVHSGVST DPQPLKEQPALNDSRYCLSSRLRVSATFWQNPRNHFRC QVQFYGLSENDEWTQDRAKPVTQIVSAEAWGRADCGF TSESYQQGVLSATILYEILLGKATLYAVLVSALVLMAMV KRKDSRG
23	R10P1A7 alpha chain	MKTFAGFSFLFLWLQLDCMSRGEDVEQSLFLSVREGDSS VINCTYTDSSSTYLWYKQEPGAGLQLLTYIFSNMDMK QDQRLTVLLNKDKHLSLRIADTQTGDSAIYFCAESKET RLMFGDGTQLVVKPNIQNPDP AVYQLRDSKSSDKSVCL FTDFDSQTNVSQSKDSDVYITDKTVLDMRSMDFKSNSA VAWSNKSDFACANAFNNSIIPEDTFFPSPESSCDVKLVEK SFETDTNLFQNL SVIGFRILLK VAGFNLLMTLRLWSS

24	R10P1A7 beta chain	MLLLLLLLGPGISLLLPGLAGSGLGAWSQHPSVWICKS GTSVKIECRSLDFQATTMFWYRQFPKQSLMLMATSNEG SKATYEQGVEKDKFLINHASLTLSTLTVTSAHPEDSSFYI CSARAGGHEQFFGPGTRLTVLEDLKNVFPPEVAVFEPSE AEISHTQKATLVCLATGFYPDHVELSWVWNGKEVHSGV STDPQPLKEQPALNDSRYCLSSRLRVSATFWQNPRNHFR CQVQFYGLSENDEWTQDRAKPVTQIVSAEAWGRADCG FTSESYQQGVLSATILYEILLGKATLYAVLV SALVLMAM VKRKDSRG
25	R4P1D10 alpha chain	MKSLRVLLVILWLQLSWVWSQQKEVEQNSGPLSVPEGA IASLNCTYSDRGSQSFFWYRQYSGKSPELIMFIYSNGDKE DGRFTAQLNKASQYVSLLRDSQPSDSATYLCVNFHDK IIFGKGTRLHILPNIQNPDPAVYQLRDSKSSDKSVCLFTDF DSQTNVSQSKSDSVYITDKTVLDMRSMDFKSNSAVAWS NKSDFACANAFNNSIIPEDTFFPSPESSCDVKLVEKSFETD TNLNFQNL SVIGFRILLK VAGFNLLMTLRLWSS
26	R4P1D10 beta chain	MGFRLLCCVAFCLLGAGPVDSGVTQTPKHLITATGQRV TLRCSRSGDLSVYWYQQSLDQGLQFLIHYNGEERAK GNILERFSAQQFPLHSELNLSSLELGDSALYFCASSVAS AYGYTFGSGTRLTVVEDLNKVPPEVAVFEPSEAEISHT QKATLVCLATGFFPDHVELSWVWNGKEVHSGVSTDPQP LKEQPALNDSRYCLSSRLRVSATFWQNPRNHFR CQVQF YGLSENDEWTQDRAKPVTQIVSAEAWGRADCGFTSVSY QQGVLSATILYEILLGKATLYAVLV SALVLMAMVKRKD F
27	R4P3F9 alpha chain	MKSLRVLLVILWLQLSWVWSQQKEVEQNSGPLSVPEGA IASLNCTYSDRGSQSFFWYRQYSGKSPELIMFIYSNGDKE DGRFTAQLNKASQYVSLLRDSQPSDSATYLCAAYSGAG SYQLTFGKGTKLSVIPNIQNPDPAVYQLRDSKSSDKSVC LFTDFDSQTNVSQSKSDSVYITDKTVLDMRSMDFKSNS AVAWSNKSDFACANAFNNSIIPEDTFFPSPESSCDVKLVE KSFETDTNLNFQNL SVIGFRILLK VAGFNLLMTLRLWSS
28	R4P3F9 beta chain	MGFRLLCCVAFCLLGAGPVDSGVTQTPKHLITATGQRV TLRCSRSGDLSVYWYQQSLDQGLQFLIQYYNGEERAK

		GNILERFSAQQFPDLHSELNLSSLELGDSALYFCASSVES SYGYTFGSGTRLTVVEDLNKVPPEVAVFEPSEAEISHTQ KATLVCLATGFFPDHVELSWVWNGKEVHSGVSTDPQPL KEQPALNDSRYCLSSRLRVSATFWQNPRNHFRCQVQFY GLSENDEWTQDRAKPVTQIVSAEAWGRADCGFTSVSYQ QGVLSATILYEILLGKATLYAVLV SALVLMAMVKRKDF
29	R4P3H3 alpha chain	MKSLRVLLVILWLQLSWVWSQQKEVEQNSGPLSVPEGA IASLNCTYSDRGSSQFFWYRQYSGKSPELIMFIYSNGDKE DGRFTAQLNKASQYVSLIRDSQPSDSATYLCVAKAGN QFYFGTGTSLTVIPNIQNPDPAVYQLRDSKSSDKSVCLFT DFDSQTNVSQSKSDVYITDKTVLDMRSMDFKSNSAVA WSNKSDFACANAFNNSIIPEDTFFPSPRESSCDVKLVEKSF ETDTNLFQNL SVIGFRILLK VAGFNLLMTLRLWSS
30	R4P3H3 beta chain	MGTRLLCWVVLGFLGTDHTGAGVSQSPRYKVAKRGQD VALRCDPISGHVSLFWYQQALGQGPEFLTYFQNEAQLD KSGLPDRFFAERPEGSVSTLKIQRTOQEDSAVYLCASSL LTSGGDNEQFFGPGTRLTVLEDLKNVPPEVAVFEPSEA EISHTQKATLVCLATGFYPDHVELSWVWNGKEVHSGVS TDPQPLKEQPALNDSRYCLSSRLRVSATFWQNPRNHFRC QVQFYGLSENDEWTQDRAKPVTQIVSAEAWGRADCGF TSESYQQGVLSATILYEILLGKATLYAVLV SALVLMAMV KRKDSRG
31	R36P3F9 alpha chain	METLLGVSLVILWLQLARVNSQQGEEDPQALSIQEGENA TMNCSYKTSINN LQWYRQNSGRGLVHLILIRSNEREKHS GRLRVTLDTSKKSSSLLITASRAADTASYFCATVSNYQLI WGAGTKLIIKPDIQNPDPAVYQLRDSKSSDKSVCLFTDF DSQTNVSQSKSDVYITDKTVLDMRSMDFKSNSAVAWS NKSDFACANAFNNSIIPEDTFFPSPRESSCDVKLVEKSFETD TNLNFQNL SVIGFRILLK VAGFNLLMTLRLWSS
32	R36P3F9 beta chain	MGPQLLGYVVLCLLGAGPLEAQVTQNPRYLITVTGKKL TVTCSQNMNHEYMSWYRQDPGLGLRQIYYSMNVEVTD KGDVPEGYK VSRKEKRNFLILESPSPNQTSLYFCASSST SGGLSGETQYFGPGTRLLVLEDLKNVPPEVAVFEPSEA EISHTQKATLVCLATGFYPDHVELSWVWNGKEVHSGVS

		TDPQPLKEQPALNDSRYCLSSRLRVSATFWQNPRNHFR CQVQFYGLSENDEWTQDRAKPVTQIVSAEAWGRADCGF TSESYQQGVLSATILYEILLGKATLYAVLVSAVLMMAMV KRKDSRG
33	R52P2G11 alpha chain	MKKHLTTFLVILWLYFYRGNGKNQVEQSPQSLIILEGKN CTLQCNYTVSPFSNLRWYKQDTGRGPVSLTIMTFSENTK SNGRYTATLDADTKQSSLHITASQLSDSASYICVVSAYG KLQFGAGTQVVVTPDIQNPDPAVYQLRDSKSSDKSVCLF TDFDSQTNVSQSKDSDVYITDKTVLDMRSMDFKSNSAV AWSNKSDFACANAFNNSIIPEDTFFPSPESSCDVKLVEKS FETDTNLNLFQNL SVIGFRILLK VAGFNLLMTLRLWSS
34	R52P2G11 beta chain	MDSWTFCCVSLCILVAKHTDAGVIQSPRHEVTEMGQEV TLRCKPISGHNSLFWYRQTMMRGLELLIYFNNNPIDDS GMPEDRFSAKMPNASFSTLKIQPSEPRDSAVYFCASSLGS PDGNQPQHFGDGTRL SILEDLNKVFPPEVAVFEPSEAEIS HTQKATLVCLATGFFPDHVELSWWVNGKEVHSGVSTD PQPLKEQPALNDSRYCLSSRLRVSATFWQNPRNHFR CQVQFYGLSENDEWTQDRAKPVTQIVSAEAWGRADCGFTS VSYQQGVLSATILYEILLGKATLYAVLVSAVLMMAMVK RKDF
35	R53P2A9 alpha chain	MACPGFLWALVISTCLEFSMAQTVTQSQPEMSVQEAET VTLSCITYDTSESDYYLFWYKQPPSRQMILVIRQEAYKQQ NATENRFSVNFQKAASFSLKISDSQLGDAAMYFCAYN SYAGGTSYGKLTFGQGTLTVHPNIQNPDPAVYQLRDSK SSDKSVCLFTDFDSQTNVSQSKDSDVYITDKTVLDMRS MDFKSNSAVAWSNKSDFACANAFNNSIIPEDTFFPSPESS CDVKLVEKS FETDTNLNLFQNL SVIGFRILLK VAGFNLL MTLRLWSS
36	R53P2A9 beta chain	MGPGLLCWVLLCLLGAGPVDAGVTQSPTHLIKTRGQQV TLRCSPISGHKSVSWYQQVLGQGPQFIFQYYEKEERGRG NFPDRFSARQFPNYSSELNVNALLGDSALYLCASSLDG TSEQYFGPGTRLTVTEDLKNVFPPEVAVFEPSEAEISHTQ KATLVCLATGFYPDHVELSWWVNGKEVHSGVSTDPQP LKEQPALNDSRYCLSSRLRVSATFWQNPRNHFR CQVQF

		YGLSENDEWTQDRAKPVTQIVSAEAWGRADCGFTSESY QQGVLSATILYEILLGKATLYAVLVSALVLMAMVKRKD SRG
37	R26P1A9 alpha chain	METLLGVSLVILWLQLARVNSQQGEEDPQALSIQEGENA TMNCSYKTSINNQLQWYRQNSGRGLVHLILRSNEREKHS GRLRVTLDTSKKSSSLITASRAADTASYFCLIGASGSR TFGEGTQLTVNPDIQNPDAVYQLRDSKSSDKSVCLFTD FDSQTNVSQSKSDVYITDKTVLDMRSMDFKSNSAVAW SNKSDFACANAFNNSIIPEDTFFPSPESSCDVKLVEKSFET DTNLFQNL SVIGFRILLKLVAGFNLLMTLRLWSS
38	R26P1A9 beta chain	MGSWTLCCVSLCILVAKHTDAGVIQSPRHEVTEMGQEV TLRCKPISGHDYLFWYRQTMMRGLELLIYFNNNVPIDDS GMPEDRFSAKMPNASFSTLKIQPSEPRDSAVYFCASSYF GWNEKLFFGSGTQLSVLEDLNKVPPEVAVFEPSEAEIS HTQKATLVCLATGFFPDHVELSWWVNGKEVHSGVSTD PQPLKEQPALNDSRYCLSSRLRVSATFWQNPRNHFRCQ VQFYGLSENDEWTQDRAKPVTQIVSAEAWGRADCGFTS VSYQQGVLSATILYEILLGKATLYAVLVSALVLMAMVK RKDF
39	R26P2A6 alpha chain	MMKSLRVLLVILWLQLSWVWSQQKEVEQDPGPLSVPE GAIVSLNCTYSNSAFQYFMWYRQYSRKGPPELLMYTYSS GNKEDGRFTAQVDKSSKYISLFIRDSQPSDSATYLCAMS DVSGGYNKLIFGAGTRLAVHPYIQNPDAVYQLRDSKSS DKSVCLFTDFDSQTNVSQSKSDVYITDKTVLDMRSM FKSNSAVAWSNKSDFAFANFNNSIIPEDTFFPSPESSCD VKLVEKSFETDTNLFQNL SVIGFRILLKLVAGFNLLMT LRLWSS
40	R26P2A6 beta chain	MGPQLLGYVVLCLLGAGPLEAQVTQNPRYLITVTGKKL TVTCSQNMNHEYMSWYRQDPGLGLRQIYYSMNVEVTD KGDVPEGYKVS RKEKRNFLILESPSPNQTSLYFCSTTP DGTDEQFFGPGTRLTVLEDLKNVPPEVAVFEPSEAEISH TQKATLVCLATGFYPDHVELSWWVNGKEVHSGVSTD PQPLKEQPALNDSRYCLSSRLRVSATFWQNPRNHFRCQV QFYGLSENDEWTQDRAKPVTQIVSAEAWGRADCGFTSE

		SYQQGVLSATILYEILLGKATLYAVLVSALVLMAMVKR KDSRG
41	R26P3H1 alpha chain	MASAPISMLAMLF TLSGLRAQSVAQPEDQVNVAEGNPL TVKCTYSVSGNPYLFWYVQYPNRGLQFLLKYITGDNLV KGSYGFEAEFNKSQTSFHLKKPSALVSDSALYFC AVR MNRDDKIIFGKGTRLHILPNIQNPDPAVYQLRDSKSSDKS VCLFTDFDSQTNVSQSKSDVYITDKTVLDMRSMDFKS NSAVAWSNKSDFACANAFNNSIIPEDTFFPSPESSCDVKL VEKSFETDTNLFQNL SVIGFRILLKLVAGFNLLMTLRL WSS
42	R26P3H1 beta chain	MSNQVLCCVFLCFLGANTVDGGITQSPKYLFRKEGQNV TLSCEQNLNHDAMYWYRQDPGQGLRLIYYSQIVNDFQK GDIAEGYSVSREKKESFPLTVTSAQKNPTAFYLCASSRA EGGEQYFGPGTRLTVTEDLKNVFPPEVAVFEPSEAEISHT QKATLVCLATGFYPDHVELSWWVNGKEVHSGVSTD PQ PLKEQPALNDSRYCLSSRLRVSATFWQNPRNHFRQCQVQ FYGLSENDEWTQDRAKPVTQIVSAEAWGRADCGFTSES YQQGVLSATILYEILLGKATLYAVLVSALVLMAMVKRK DSRG
43	R35P3A4 alpha chain	MTSIRAVFIFLWLQLDLVNGENVEQHPSTLSVQEGDSAV IKCTYSDSASNYFPWYKQELGKRPQLIIDIRSNVGEKKD QRIAVTLNKTAKHFS LHITETQPEDSAVYFCAASPTGGY NKLIFGAGTRLAVHPYIQNPDP AVYQLRDSKSSDKSVCL FTDFDSQTNVSQSKSDVYITDKTVLDMRSMDFKSNSA VAWSNKSDFACANAFNNSIIPEDTFFPSPESSCDVKLVEK SFETDTNLFQNL SVIGFRILLKLVAGFNLLMTLRLWSS
44	R35P3A4 beta chain	MSIGLLCCAALSLLWAGPVNAGVTQTPKFQVLKTGQSM TLQCAQDMNHEYMSWYRQDPGMGLRLIHYSVGAGITD QGEVPNGYNVSRSTTEDFPLRLLSAAPSQTSVYFCASSL GGASQEYFGPGTRLTVTEDLKNVFPPEVAVFEPSEAEIS HTQKATLVCLATGFYPDHVELSWWVNGKEVHSGVSTD PQPLKEQPALNDSRYCLSSRLRVSATFWQNPRNHFRCC VQFYGLSENDEWTQDRAKPVTQIVSAEAWGRADCGFTS

		ESYQQGVLSATILYEILLGKATLYAVLVSALVLMAMVK RKDSRG
45	R37P1C9 alpha chain	MKLVTSITVLLSLGIMGDAKTTQPNSMESNEEEPVHLPC NHSTISGTDYIHWYRQLPSQGPEYVIHGLTSNVNNRMAS LAIAEDRKSSTLILHRATLRDAAVYYCILFNFNKFYFGSG TKLNVKPNIQNPDPVYQLRDSKSSDKSVCLFTDFDSQT NVSQSKDSDVYITDKTVLDMRSMDFKSNSAVAWSNKS DFACANAFNNSIIPEDTFFPSPESSCDVKLVEKSFETDTNL NFQNLSVIGFRILLKLVAGFNLLMTLRLWSS
46	R37P1C9 beta chain	MGPGLLHWMALCLLGTGHGDAMVIQNPRYQVTQFGKP VTLSCSQTLNHNVMYWYQQKSSQAPKLLFHYYDKDFN NEADTPDNFQSRPNTSFCFLDIRSPGLGDAAMYL CATS SGETNEKLFFGSGTQLSVLEDLNKVPPEVAVFEPSEAEI SHTQKATLVCLATGFFPDHVELSWWVNGKEVHSGVST DPQPLKEQPALNDSRYCLSSRLRV SATFWQNPRNHFRC QVQFYGLSENDEWTQDRAKPVTQIVSAEAWGRADCGF TSVSYQQGVLSATILYEILLGKATLYAVLVSALVLMAM VKRKDF
47	R37P1H1 alpha chain	MTRVSLWAVVVSTCLESMAQTVTQSQPEMSVQEAE TVTL SCTYDTSESNYLFWYKQPPSRQMILVIRQEAYKQ QNATENRFSVNFQKA AKSFSLKISDSQLGDTAMYFCAFG YSGGGADGLTFGKGTHLIQPYIQNPDPVYQLRDSKSS DKSVCLFTDFDSQTNVSQSKDSDVYITDKTVLDMRSM FKSNSAVAWSNKSD FACANAFNNSIIPEDTFFPSPESSCD VKLVEKSFETDTNLNFQNLSVIGFRILLKLVAGFNLLMT LRLWSS
48	R37P1H1 beta chain	MGPGLLCWALLCLLGAGLVDAGVTQSPTHLIKTRGQQV TLRCSPKSGHDTVSWYQQALGQGPQFIFQYEEEEERQR GNFPDRFSGHQFPNYSSELNVNALLLGDSALYLCASSNE GQGWEAEAFFGQGTRLTVVEDLNKVPPEVAVFEPSEA EISHTQKATLVCLATGFFPDHVELSWWVNGKEVHSGVS TDPQPLKEQPALNDSRYCLSSRLRV SATFWQNPRNHFRC QVQFYGLSENDEWTQDRAKPVTQIVSAEAWGRADCGF

		TSVSYQQGVLSATILYEILLGKATLYAVLVSAVLMMAM VKRKDF
49	R42P3A9 alpha chain	MKRILGALLGLLSAQVCCVRGIQVEQSPDLILQEGANS TLRCNFSDSVNNLQWFHQNPWGQLINLFYIPSGTKQNG RLSATTVATERYSLLYISSSQTTDSGVYFCAVHNFNKFY FGSGTKLNVKPNIQNPDAVYQLRDSKSSDKSVCLFTDF DSQTNVSQSKDSDVYITDKTVLDMRSMDFKSNSAVAWS NKSDFACANAFNNSIIPEDTFFPSPESSCDVKLVEKSFETD TNLNFQNLSVIGFRILLKLVAGFNLLMTLRLWSS
50	R42P3A9 beta chain	MLSPDLPDSAWNTRLLCHVMLCLLGAVSVAAGVIQSPR HLIKEKRETATLKCYPPIRHDTVYWYQQGPGQDPQFLIS FYEKMQSDKGSIPDRFSAQQFSDYHSELNMSSLELGDSA LYFCASSLLGQGYNEQFFGPGTRLTVLEDLKNVFPPEVA VFEPSEAEISHTQKATLVCLATGFYPDHVELSWWVNGK EVHSGVSTDPQPLKEQPALNDSRYCLSSRLRVSATFWQN PRNHFRQCQVQFYGLSENDEWTQDRAKPVTQIVSAEAWG RADCGFTSESYQQGVLSATILYEILLGKATLYAVLVSA VLMAMVKRKDSRG
51	R43P3F2 alpha chain	MLTASLLRAVIASICVVSSMAQKVTQAQTEISVVEKEDV TLDCVYETRDTTYLFWYKQPPSGELVFLIRNSFDEQN EISGRYSWNFQKSTSSFNFTITASQVVDSAVYFCALSNN NAGNMLTFGGGTRLVMKPHIQNPDAVYQLRDSKSSDK SVCLFTDFDSQTNVSQSKDSDVYITDKTVLDMRSMDFK SNSAVAWSNKSDFACANAFNNSIIPEDTFFPSPESSCDVK LVEKSFETDTNLNFQNLSVIGFRILLKLVAGFNLLMTLRL WSS
52	R43P3F2 beta chain	MLSPDLPDSAWNTRLLCHVMLCLLGAVSVAAGVIQSPR HLIKEKRETATLKCYPPIRHDTVYWYQQGPGQDPQFLIS FYEKMQSDKGSIPDRFSAQQFSDYHSELNMSSLELGDSA LYFCASSPTGTSGYNEQFFGPGTRLTVLEDLKNVFPPEV AVFEPSEAEISHTQKATLVCLATGFYPDHVELSWWVNG KEVHSGVSTDPQPLKEQPALNDSRYCLSSRLRVSATFWQ NPRNHFRQCQVQFYGLSENDEWTQDRAKPVTQIVSAEAW

		GRADCGFTSESYQQGVLSATILYEILLGKATLYAVLVSA LVLMMAMVKRKDSRG
53	R43P3G5 alpha chain	MEKNPLAAPLLILWFHLDCVSSILNVEQSPQSLHVQEGD STNFTCSFPSSNFYALHWYRWETAKSPEALFVMTLNGD EKKKGRISATLNTKEGYSYLYIKGSQPEDSATYLCALNR DDKIIFGKGTRLHLIPNIQNPDPVYQLRDSKSSDKSVCL FTDFDSQTNVSQSKSDVYITDKTVLDMRSMDFKSNSA VAWSNKSDFACANAFNNSIIPEDTFFPSPESSCDVKLVEK SFETDTNLNFQNL SVIGFRILLKLVAGFNLLMTLRLWSS
54	R43P3G5 beta chain	MGIRLLCRVAFCLAVGLVDVKVTQSSRYLVKRTGEKV FLECVQDMDHENMFWYRQDPGLGLRLIYFSYDVKMKE KGDIEGYSVSREKKERFSLILESASTNQTSMYLCASRLP SRTYEQYFGPGTRLTVTEDLKNVFPPEVAVFEPSEAEISH TQKATLVCLATGFYPDHVELSWWVNGKEVHSGVSTDP QPLKEQPALNDSRYCLSSRLRVSATFWQNPRNHFRCQV QFYGLSENDEWTQDRAKPVTQIVSAEAWGRADCGFTSE SYQQGVLSATILYEILLGKATLYAVLVSA LVLMMAMVKR KDSRG
55	R59P2E7 alpha chain	METLLGILLWLQLQWVSSKQEVTPIPAALSVPEGENLV LNCSTDSAIYNLQWFRQDPGKGLTSLLLIQSSQREQTSG RLNASLDKSSGRSTLYIAASQPGDSATYLCVNSDYKLS FGAGTTVTVRANIQNPDPVYQLRDSKSSDKSVCLFTDF DSQTNVSQSKSDVYITDKTVLDMRSMDFKSNSA VAWS NKSDFACANAFNNSIIPEDTFFPSPESSCDVKLVEKSFETD TNLNFQNL SVIGFRILLKLVAGFNLLMTLRLWSS
56	R59P2E7 beta chain	MLSPDLPDSAWNTRLLCHVMLCLLGAVSVAAGVIQSPR HLIKEKRETATLKCYPPIRHDTVYWYQQGPGQDPQFLIS FYEKMQSDKGSIPDRFSAQQFSDYHSELNMSSLELGDSA LYFCASSLGLGTGDYGYTFGSGTRLTVVEDLNKVPPEV AVFEPSEAEISHTQKATLVCLATGFFPDHVELSWWVNG KEVHSGVSTDPQPLKEQPALNDSRYCLSSRLRVSATFWQ NPRNHFRCQVQFYGLSENDEWTQDRAKPVTQIVSAEAW GRADCGFTSVSYQQGVLSATILYEILLGKATLYAVLVSA LVLMMAMVKRKDF

57	R11P3D3 alpha chain	MEKNPLAAPLLILWFHLD CVSSILNVEQSPQSLHVQEGD STNFTCSFPSSNFYALHWYRWETAKSPEALFVMTLNGD EKKKGRISATLNTKEGYSYLYIKGSQPEDSATYLCALYN NNDMRFGAGTRLTVKPNIQNPDP AVYQLRDSKSSDKSV CLFTDFDSQTNVSQSKDSDVYITDKTVLDMRSMDFKSN SAVAWSNKSDFACANAFNNSIIPEDTFFPSPESSCDVKLV EKSFETDTNLFQNL SVIGFRILLKLVAGFNLLMTLRLW SS
58	R11P3D3 beta chain	MDSWTFCCVSLCILVAKHTDAGVIQSPRHEVTEMGQEV TLRCKPISGHNSLFWYRQTM MRGLELLIYFNNNPIDDS GMPEDRFS AKMPNASFSTLKIQPSEPRDS AVYFCASSPGS TDTQYFGPGTRLTVLEDLKNVFPPEVAVFEPSEAEISHTQ KATLVCLATGFYPDHVELSWWVNGKEVHSGVSTDPQP LKEQPALNDSRYCLSSRLRVSATFWQNPRNHFRCQVQF YGLSENDEWTQDRAKPVTQIVSAEAWGRADCGFTSESY QQGVLSATILYEILLGKATLYAVLVSALVLMAMVKRKD SRG
59	R16P1C10 alpha chain	MKSLRVLLVILWLQLSWVWSQQKEVEQNSGPLSVPEGA IASLNCTYSDRGSQSFFWYRQYSGKSPELIMFIYSNGDKE DGRFTAQLNKASQYVSLLRDSQPSDSATYLCAAVISNF GNEKLTFGTGTRLTIIPNIQNPDP AVYQLRDSKSSDKSVC LFTDFDSQTNVSQSKDSDVYITDKTVLDMRSMDFKSN AVAWSNKSDFACANAFNNSIIPEDTFFPSPESSCDVKLVE KSFETDTNLFQNL SVIGFRILLKLVAGFNLLMTLRLWSS
60	R16P1C10 beta chain	MGSRLLCWVLLCLLGAGPVKAGVTQTTRYLIKTRGQQV TLSCSPISGHRVSWSYQQTPGQGLQFLFEYFSETQRNKG NFPGRFSGRQFSNSRSEMNVSLELGDSALYLCASSPWD SPNEQYFGPGTRLTVTEDLKNVFPPEVAVFEPSEAEISHT QKATLVCLATGFYPDHVELSWWVNGKEVHSGVSTDPQ PLKEQPALNDSRYCLSSRLRVSATFWQNPRNHFRCQVQ FYGLSENDEWTQDRAKPVTQIVSAEAWGRADCGFTSES YQQGVLSATILYEILLGKATLYAVLVSALVLMAMVKRK DSRG

61	R16P1E8 alpha chain	MMKSLRVLLVILWLQLSWVWSQQKEVEQDPGPLSVPE GAIVSLNCTYSNSAFQYFMWYRQYSRKGPPELLMYTYSS GNKEDGRFTAQVDKSSKYISLFIRDSQPSDSATYLCAMS EAAGNKLTFGGGTRVLVKPNIQNPDPAVYQLRDSKSSD KSVCLFTDFDSQTNVSQSKSDVYITDKTVLDMRSMDF KSNSAVAWSNKSDFACANAFNNSIIPEDTFFPSPRESSCDV KLVEKSFETDTNLFQNLVIGFRILLKLVAGFNLLMTLR LWSS
62	R16P1E8 beta chain	MGTRLLCWAALCLLGAELTEAGVAQSPRYKIIKRQSV AFWCNPISGHATLYWYQQILGQGPKLLIQFQNNGVVDD SQLPKDRFSAERLKGVDSTLKIQPAKLEDSAVYLCASSY TNQGEAFFGQGTRLTVVEDLNKVPPEVAVFEPSEAEIS HTQKATLVCLATGFFPDHVELSWWVNGKEVHSGVSTD PQPLKEQPALNDSRYCLSSRLRVSATFWQNPRNHFRQC VQFYGLSENDEWTQDRAKPVTQIVSAEAWGRADCGFTS VSYQQGVLSATILYEILLGKATLYAVLVLSALVLMAMVK RKDF
63	R17P1A9 alpha chain	MKSLRVLLVILWLQLSWVWSQQKEVEQNSGPLSVPEGA IASLNCTYSDRGSQSFFWYRQYSGKSPELIMSIYSNGDKE DGRFTAQLNKASQYVSLIRDSQPSDSATYLCVNLQA GTALIFGKGTTLSVSSNIQNPDPAVYQLRDSKSSDKSVCL FTDFDSQTNVSQSKSDVYITDKTVLDMRSMDFKSNSA VAWSNKSDFACANAFNNSIIPEDTFFPSPRESSCDVKLVEK SFETDTNLFQNLVIGFRILLKLVAGFNLLMTLRLWSS
64	R17P1A9 beta chain	MGFRLLCCVAFCLLGAAGPVDSGVTQTPKHLITATGQRV TLRCSPRSGDLVYWYQQSLDQGLQFLIQYYNGEERAK GNILERFSAQQFDDLHSELNLSSLELGDSALYFCASSAET GPWLGNEQFFGPGTRLTVLEDLKNVPPEVAVFEPSEAE ISHTQKATLVCLATGFYPDHVELSWWVNGKEVHSGVST DPQPLKEQPALNDSRYCLSSRLRVSATFWQNPRNHFRQC QVQFYGLSENDEWTQDRAKPVTQIVSAEAWGRADCGF TSESYQQGVLSATILYEILLGKATLYAVLVLSALVLMAMV KRKDSRG

65	R17P1D7 alpha chain	MACPGFLWALVISTCLEFSMAQTVTQSQPEMSVQEAET VTLSCTYDTSESDYYLFWYKQPPSRQMILVIRQEAYKQQ NATENRFSVNFQKAASFSLKISDSQLGDAAMYFCAYR WAQGGSEKL VFGKGTKLTVNPYIQKPDPAVYQLRDSKS SDKSVCLFTDFDSQTNVSQSKSDSVYITDKTVLDMRSM DFKSNSAVAWSNKSDFACANAFNNSIIPEDTFFPSPESSC DVKLVEKSFETDTNLFQNL SVIGFRILLK VAGFNLLM TLRLWSS
66	R17P1D7 beta chain	MTIRLLCYMGFYFLGAGLMEADYQTPRYLVIGTGKKIT LECSQTMGHDKMYWYQQDPGMELHLIHYSYGVNSTEK GDLSSSESTVSRIRTEHFPLTLESARPSHTSQYLCATELWS SGGTGELFFGEGSRLTVLEDLKNVFPPEVAVFEPSEAEIS HTQKATLVCLATGFYDPDHVELSWWVNGKEVHSGVSTD PQPLKEQPALNDSRYCLSSRLRVSATFWQNPRNHFRCQ VQFYGLSENDEWTQDRAKPVTQIVSAEAWGRADCGFTS ESYQQGVLSATILYEILLGKATLYAVLVSALVLMAMVK RKDSRG
67	R17P1G3 alpha chain	MKSLRVLLVILWLQLSWVWSQQKEVEQNSGPLSVPEGA IASLNCTYSDRGSSQFFWYRQYSGKSPELMSIYSNGDKE DGRFTAQLNKASQYVSLLRDSQPSDSATYLCVAGPSGT YKYIFGTGTRLKVLANIQNPDPAVYQLRDSKSSDKSVCL FTDFDSQTNVSQSKSDSVYITDKTVLDMRSMDFKSNSA VAWSNKSDFACANAFNNSIIPEDTFFPSPESSCDVKLVEK SFETDTNLFQNL SVIGFRILLK VAGFNLLMTLRLWSS
68	R17P1G3 beta chain	MGPQLLG YVVLCLLGAGPLEAQVTQNPRYLITVTGKKL TVTCSQNMNHEYMSWYRQDPGLGLRQIYYSMNVEVTD KGDVPEGYK VSRKEKRNFLILESPSPNQTSLYFCASSPG GSGNEQFFGPGTRLTVLEDLKNVFPPEVAVFEPSEAEISH TQKATLVCLATGFYDPDHVELSWWVNGKEVHSGVSTDP QPLKEQPALNDSRYCLSSRLRVSATFWQNPRNHFRCQV QFYGLSENDEWTQDRAKPVTQIVSAEAWGRADCGFTSE SYQQGVLSATILYEILLGKATLYAVLVSALVLMAMVKR KDSRG

69	R17P2B6 alpha chain	MKSLRVLLVILWLQLSWVWSQQKEVEQNSGPLSVPEGA IASLNCTYSDRGSQSFFWYRQYSGKSPELIMFIYSNGDKE DGRFTAQLNKASQYVSLLRDSQPSDSATYLCVVSGGG ADGLTFGKGTHLIQPYIQKPDPAVYQLRDSKSSDKSVCL FTDFDSQTNVSQSKSDVYITDKTVLDMRSMDFKSNSA VAWSNKSDFACANAFNNSIIPEDTFFPSPESSCDVKLVEK SFETDTNLFQNL SVIGFRILLKLVAGFNLLMTLRLWSS
70	R17P2B6 beta chain	MLSPDLPSAWNTRLLCHVMLCLLGAVSVAAGVIQSPR HLIKEKRETATLKCYPPIRHDTVYWYQQGPGQDPQFLIS FYEKMQSDKGSIPDRFSAQQFSDYHSELNMSSLELGD LYFCASSLGRGGQPQHFGDGTRLSELEDLNKVFPEVAV FEPSEAEISHTQKATLVCLATGFFPDHVELSWVNGKEV HSGVSTDPQPLKEQPALNDSRYCLSSRLRVSATFWQNPR NHFRCQVQFYGLSENDEWTQDRAKPVTVIVSAEAWGR ADCGFTSVSYQQGVLSATILYEILLGKATLYAVLVSA LMAMVVRKDF
71	R11P3D3KE alpha chain	MEKNPLAAPLLILWFHLDCVSSILNVEQSPQSLHVQEGD STNFTCSFPSSNFYALHWYRKETAKSPEALFVMTLNGDE KKKGRISATLNTKEGYSLYIKGSQPEDSATYLCALYNN NDMRFGAGTRLTVKPNIQNPDPVYQLRDSKSSDKSVC LFTDFDSQTNVSQSKSDVYITDKTVLDMRSMDFKSNS AVAWSNKSDFACANAFNNSIIPEDTFFPSPESSCDVKLVE KSFETDTNLFQNL SVIGFRILLKLVAGFNLLMTLRLWSS
72	R11KEA alpha chain nucleic acid sequence	atggagaagaatccccctggctgccccctgctgatcctgtggtttcacctggactgcgtgt cctctatcctgaatgtggaacagagccacagagcctgcacgtgcaggaggcgactc caccacttcacatgctcttttctagctccaacttctacgacctgcactggtagagaaagg agaccgcaaagtccccagaggccctgttcgtgatgacactgaacggcgatgagaagaa gaaggccgcacagcgccaccctgaatacaaaggagggtactcctatctgtacatca agggtcccagcctgaggactctgccacctatctgtgcgcctgtacaacaataacgata tgcggtttggcgccggcaccagactgacagtgaagccaaacatccagaatccagacc cgccgtgtatcagctgcgggacagcaagtctagcgataagagcgtgtgcctgttcaccg actttgattctcagacaaacgtgagccagccaaggacagcgacgtgtacatcaccgaca agacagtgtggatatgagaagcatggacttcaagttaacagcgccgtggcctgtgctc aataagtctgatttcgctgcgccaatgccttaataactccatcatccccgaggataccttc

		tttccttctccagagtcctcttgtgacgtgaagctggaggagaagtctttcagaccgatac aaacctgaattttcagaacctgagcgtgatcggcttcaggatcctgctgctgaaggtggcc ggctttaatctgctgatgacctgaggctgtggagctcc
73	R11KEA beta chain nucleic acid sequence	atggactcttgaccttctgctgctgagcctgtgcatcctggaggccaagcacacagac gccggcgtgatccagtccttaggcacgaggtgaccgagatgggccaggaggtgaca ctgctgctgaagccaatctctggccacaacagcctgttttggtataggagaccatgatgc gcggcctggagctgctgatctactcaataacaatgtgcccacgacgattccggcatgcc tgaggatcgggtttctgccaagatgccaatgccagcttctccacactgaagatccagcct agcgagccaagagactccgccgtgtattttgccccttagcccaggcagcaccgatac acagtacttcggaccaggaaccaggctgacagtgtggaggacctgaagaacgtgtcc cccctgaggtggccgtgtttgagccctctgaggccgagatcagccacaccagaaggc caccctggtgtgcttggaaccggcttctatcctgatcacgtggagctgtcctggtgggtg aacggcaaggaggtgcacagcggcgtgtccacagaccacagcccctgaaggagca gccagccctgaatgatagccggtattgcctgtcctctcggctgagagtgtccgccaccttt ggcagaacccccgaatcacttcagatgtcaggtgcagtttacggcctgtccgagaacg atgagtggaaccaggaccgggccaagcctgtgacacagatcgtgtctgccgagcatg gggaagagcagactgtggcttcacctctgagagctaccagcaggcgtgctgagcgcc accatcctgtatgagatcctgctgggcaaggccacactgtacgccgtctgtctccgctc tggtgctgatggcaatggtcaaaagaaaagatagtcgggga
74	R39P1C12 beta chain	MGPGLLCWALLCLLGAGLVDAGVTQSPTHLIKTRGQQV TLRCSPKSGHDTVSWYQQALGQGPQFIFQYEEEEERQR GNFPDRFSGHQFPNYSSELNVNALLGDSALYLCASSQL NTEAFFGQGTRLTVVEDLNKVFPEVAVFEPSEAEISHTQ KATLVCLATGFFPDHVELSWWVNGKEVHSGVSTDPQPL KEQPALNDSRYCLSSRLRVSATFWQNPRNHFRQVQFY GLSENDEWTQDRAKPVTQIVSAEAWGRADCGFTSVSYQ QGVLSATILYEILLGKATLYAVLVSALVLMAMVKRKDF
75	R39P1F5 alpha chain	MKSLRVLLVILWLQLSWVWSQQKEVEQNSGPLSVPEGA IASLNCTYSDRGSSQFFWYRQYSGKSPELIMFIYSNGDKE DGRFTAQLNKASQYVSLLRDSQPSDSATYLCVNNARL MFGDGTQLVVKPNIQNPDPAVYQLRDSKSSDKSVCLFT DFDSQTNVSQKSDSVYITDKTVLDMRSMDFKSNSAVA WSNKSDFACANAFNNSIIPEDTFFPSPESSCDVKLVEKSF ETDTNLFQNLVIGFRILLKLVAGFNLLMTLRLWSS

76	R39P1F5 beta chain	MDTWLVCWAIFSLLKAGLTEPEVTQTPSHQVTQMGQEV ILRCVPISNHL YFYWYRQILGQKVEFLVSFYNN EISEKSEI FDDQFSVERPDGSNFTLKIRSTKLEDSAMYFCASSGQGA NEQYFGPGTRLTVTEDLKNVFPPEVAVFEPSEAEISHTQK ATLVCLATGFYPDHVELSWWVNGKEVHSGVSTDPQPL KEQPALNDSRYCLSSRLRVSATFWQNPRNHFRCQVQFY GLSENDEWTQDRAKPVTQIVSAEAWGRADCGFTSESYQ QGVLSATILYEILLGKATLYAVLVSALVLMAMVKRKDS RG
77	R40P1C2 alpha chain	MACPGFLWALVISTCLEFSMAQTVTQSQPEMSVQEAET VTL SCTYDTSESDYYLFWYKQPPSRQMILVIRQEAYKQQ NATENRFSVNFQKA AKSFSCLKISDSQLGDAAMYFCAYL NYQLIWGAGTKLIIPDIQNPDP AVYQLRDSKSSDKSVC LFTDFDSQTNVSQSKDSDVYITDKTVLDMRSMDFKSNS AVAWSNKSDFACANAFNNSIIPEDTFFPSPESSCDVKLVE KSFETDTNLFQNL SVIGFRILLK VAGFNLLMTLRLWSS
78	R40P1C2 beta chain	MDTWLVCWAIFSLLKAGLTEPEVTQTPSHQVTQMGQEV ILRCVPISNHL YFYWYRQILGQKVEFLVSFYNN EISEKSEI FDDQFSVERPDGSNFTLKIRSTKLEDSAMYFCASSEMTA VGQYFGPGTRLTVTEDLKNVFPPEVAVFEPSEAEISHTQ KATLVCLATGFYPDHVELSWWVNGKEVHSGVSTDPQP LKEQPALNDSRYCLSSRLRVSATFWQNPRNHFRCQVQF YGLSENDEWTQDRAKPVTQIVSAEAWGRADCGFTSESY QQGVLSATILYEILLGKATLYAVLVSALVLMAMVKRKD SRG
79	R41P3E6 alpha chain	MKSLRVLLVILWLQLSWVWSQQKEVEQNSGPLSVPEGA IASLNCTYSDRGSSQFFWYRQYSGKSPELIMFIYSNGDKE DGRFT AQLNKASQYVSLLIRDSQPSDSATYLCAAFSGYALNFGK GTSLLVTPHIQNPDP AVYQLRDSKSSDKSVCLFTDFDSQ TNVSQSKDSDVYITDKTVLDMRSMDFKSNSAVAWSNKSD FACANAFNNSIIPEDTFFPSPESSCDVKLVEKSFETDTNL NFQNL SVIGFRILLK VAGFNLLMTLRLWSS

80	R41P3E6 beta chain	MDTWLVCWAIFSLLKAGLTEPEVTQTPSHQVTQMGQEV ILRCVPISNHL YFYWYRQILGQKVEFLVSFYNN EISEKSEI FDDQFSVERPDGSNFTLKIRSTKLEDSAMYFCASSQYTG ELFFGEGSRLTVLEDLKNVFPPEVAVFEPSEAEISHTQKA TLVCLATGFYPDHVELSWWVNGKEVHSGVSTDPQPLKE QPALNDSRYCLSSRLRVSATFWQNPRNHFR CQVQFYGL SENDEWTQDRAK PVTQIVSAEAWGRADCGFTSESYQQG VLSATILYEILLGKATLYAVLVSALVLMAMVKRKDSRG
81	R43P3G4 alpha chain	MKSLRVLLVILWLQLSWVWSQQKEVEQNSGPLSVPEGA IASLNCTYSDRGSQSFFWYRQYSGKSPELIMFIYSNGDKE DGRFTAQLNKASQYVSLLIRDSQPSDSATYLCVANGGD MRFGAGTRLTVKPNIQNPDP AVYQLRDSKSSDKSVCLFT DFDSQTNVSQSKDSDVYITDKTVLDMRSMDFKSNSAVA WSNKSDFACANAFNNSIIPEDTFFPSPRESSCDVKLVEKSF ETDTNLNFQNL SVIGFRILLK VAGFNLLMTLRLWSS
82	R43P3G4 beta chain	MDTWLVCWAIFSLLKAGLTEPEVTQTPSHQVTQMGQEV ILRCVPISNHL YFYWYRQILGQKVEFLVSFYNN EISEKSEI FDDQFSVERPDGSNFTLKIRSTKLEDSAMYFCASSGQGA LEQYFGPGTRLTVTEDLKNVFPPEVAVFEPSEAEISHTQK ATLVCLATGFYPDHVELSWWVNGKEVHSGVSTDPQPL KEQPALNDSRYCLSSRLRVSATFWQNPRNHFR CQVQFY GLSENDEWTQDRAK PVTQIVSAEAWGRADCGFTSESYQ QGVLSATILYEILLGKATLYAVLVSALVLMAMVKRKDS RG
83	R44P3B3 alpha chain	MAMLLGASVLILWLQPDWVNSQQKNDDQQVKQNSPSL SVQEGRISILNCDYTNSMFDYFLWYKKYPAEGPTFLISIS SIKDKNEDGRFTVFLNKSAKHL SLHIVPSQPGDSAVYFC AASGLYNQGGKLIFGQGT ELSVKPNIQNPDP AVYQLRDS KSSDKSVCLFTDFDSQTNVSQSKDSDVYITDKTVLDMRS MDFKSNSAVAWSNKSDFACANAFNNSIIPEDTFFPSPRESS CDVKLVEKSFETDTNLNFQNL SVIGFRILLK VAGFNLL MTLRLWSS
84	R44P3B3 beta chain	MGCRLCCVVFCLLQAGPLDTAVSQTPKYLVTQMGND KSIKCEQNLGHDTMYWYKQDSKKFLKIMFSYNNKELIIN

		ETVPNRFSPKSPDKAHLNLHINSLELGDSAVYFCASSLG DRGYEQYFGPGTRLTVTEDLKNVFPPEVAVFEPSEAEIS HTQKATLVCLATGFYPDHVELSWWVNGKEVHSGVSTD PQPLKEQPALNDSRYCLSSRLRVSATFWQNPRNHFRCQ VQFYGLSENDEWTQDRAKPVTQIVSAEAWGRADCGFTS ESYQQGVLSATILYEILLGKATLYAVLVSALVLMAMVK RKDSRG
85	R44P3E7 alpha chain	MKTFAGFSFLFLWLQLDCMSRGEDVEQSLFLSVREGDSS VINCTYTDSSSTYLWYKQEPGAGLQLLTYIFSNMDMK QDQRLTVLLNKKDKHLSLRIADTQTGDSAIYFCAEINNN ARLMFGDGTQLVVKPNIQNPDPAVYQLRDSKSSDKSVC LFTDFDSQTNVSQSKSDVYITDKTVLDMRSMDFKSNS AVAWSNKSDFACANAFNNSIIPEDTFFPSPESSCDVKLVE KSFETDTNLFQNLVIGFRILLKLVAGFNLLMTLRLWSS
86	R44P3E7 beta chain	MLSPDLPDSAWNTRLLCHVMLCLLGAVSVAAGVIQSPR HLIKEKRETATLKCYPPIRHDTVYWYQQGPGQDPQFLIS FYEKMQSDKGSIPDRFSAQQFSDYHSELNMSSLELGDSA LYFCASSPPDQNTQYFGPGTRLTVLEDLKNVFPPEVAVF EPSEAEISHTQKATLVCLATGFYPDHVELSWWVNGKEV HSGVSTDPQPLKEQPALNDSRYCLSSRLRVSATFWQNPR NHFRCQVQFYGLSENDEWTQDRAKPVTQIVSAEAWGR ADCGFTSESYQQGVLSATILYEILLGKATLYAVLVSALV LMAMVKRKDSRG
87	R49P2B7 alpha chain	MLLLLVPVLEVIFTLGGTRAQSVTQLGSHVSVSEGALVL LRCNYSSSVPPYLFWYVQYPNQGLQLLLKYTTGATLVK GINGFEAEFFKSETSFHLTKPSAHMSDAAEYFC AVRIFG NEKLTFGTGTRLTIIPNIQNPDPAVYQLRDSKSSDKSVCL FTDFDSQTNVSQSKSDVYITDKTVLDMRSMDFKSNSA VAWSNKSDFACANAFNNSIIPEDTFFPSPESSCDVKLVEK SFETDTNLFQNLVIGFRILLKLVAGFNLLMTLRLWSS
88	R49P2B7 beta chain	MGIRLLCRVAFCLAVGLVDVKVTQSSRYLVKRTGEKV FLECVQDMDHENMFWYRQDPGLGLRLIYFSYDVKMKE KGDIEGYSVSREKKERFSLILESASTNQTSMYLCASSLM GELTGELFFGEGSRLTVLEDLKNVFPPEVAVFEPSEAEIS

		HTQKATLVCLATGFYPDHVELSWWVNGKEVHSGVSTD PQPLKEQPALNDSRYCLSSRLRVSATFWQNPRNHFRQC VQFYGLSENDEWTQDRAKPVTQIVSAEAWGRADCGFTS ESYQQGVLSATILYEILLGKATLYAVLVSALVLMAMVK RKDSRG
89	R55P1G7 alpha chain	MMKSLRVLLVILWLQLSWVWSQQKEVEQDPGPLSVPE GAIVSLNCTYSNSAFQYFMWYRQYSRKGPPELLMYTYSS GNKEDGRFTAQVDKSSKYISLFIRDSQPSDSATYLCAMM GDTGTASKLTFGTGTRLQVTLDIQNPDPAVYQLRDSKSS DKSVCLFTDFDSQTNVSQSKDSDVYITDKTVLDMRSMDFK SNSAVAWSNKSDFACANAFNNSIIPEDTFFPSPESSCD VKLVEKSFETDTNLFQNLVIGFRILLKLVAGFNLLMT LRLWSS
90	R55P1G7 beta chain	MGIRLLCRVAFCLAVGLVDVKVTQSSRYLVKRTGEKV FLECVQMDHENMFWYRQDPGLGLRLIYFSYDVKMKE KGDIEGYSVSREKKERFSLILESASTNQTSMYLCASSFG GYEQYFGPGTRLTVTEDLKNVFPPEVAVFEPSEAEISHTQ KATLVCLATGFYPDHVELSWWVNGKEVHSGVSTDPQP LKEQPALNDSRYCLSSRLRVSATFWQNPRNHFRQCQVQF YGLSENDEWTQDRAKPVTQIVSAEAWGRADCGFTSESY QQGVLSATILYEILLGKATLYAVLVSALVLMAMVKRKD SRG
91	R59P2A7 alpha chain	MKSLRVLLVILWLQLSWVWSQQKEVEQNSGPLSVPEGA IASLNCTYSDRGSQSFFWYRQYSGKSPELIMSIYSNGDKE DGRFTAQLNKASQYVSLLRDSQPSDSATYLCAVQPHD MRFGAGTRLTVKPNIQNPDPVAVYQLRDSKSSDKSVCLFT DFDSQTNVSQSKDSDVYITDKTVLDMRSMDFKNSAVA WSNKSDFACANAFNNSIIPEDTFFPSPESSCDVKLVEKSF ETDTNLFQNLVIGFRILLKLVAGFNLLMTLRLWSS
92	R59P2A7 beta chain	MLCSLLALLLGTFFGVRSQTIHQWPATLVQPVGSPLSLE CTVEGTSNPPLYWYRQAAGRGLQLLFYSVGIGQISSEVP QNLSASRPQDRQFILSSKLLLSDSGFYLCAWSGLVAEQ FFGPGTRLTVLEDLKNVFPPEVAVFEPSEAEISHTQKATL VCLATGFYPDHVELSWWVNGKEVHSGVSTDPQPLKEQP

		ALNDSRYCLSSRLRVSATFWQNPRNHFRCQVQFYGLSE NDEWTQDRAKPVTVQIVSAEAWGRADCGFTSESYQQGV LSATILYEILLGKATLYAVLVSALVLMAMVKRKDSRG
93	P2A	ATNFSLLKQAGDVEENPGP
94	T2A	EGRGSLLTCGDVEENPGP
95	E2A	QCTNYALLKLAGDVESNPGP
96	F2A	VKQTLNFDLLKLAGDVESNPGP
97	RD114TR	MKLPTGMVILCSLIIVRAGFDDPRKAIALVQKQHGKPC CSGGQVSEAPPNSIQQVTCPGKTAYLMTNQKWKCRVTP KISPSGGELQNCPCNTFQDSMHSSCYTEYRQCRRINKTY YTATLLKIRSGSLNEVQILQNPQNQLLQSPCRGSINQVPCW SATAPIHISDGGGPLDTRVWTVQKRLEQIHKAMTPELQ YHPLALPKVRDDLSDARTFDILNTTFRLQMSNFSLAQ DCWLCLKLGTPTPLAIPTPSLTYSLADSLANASCQIIPLL VQPMQFSNSSCLSSPFINDTEQIDLGAVTFTNCTSVANVS SPLCALNGSVFLCGNNMAYTYLPQNWTRLCVQASLLPD IDINPGDEPVPIPAIDHYIHRPKRAVQFIPLLAGLGITAAFT TGATGLGVSVTQYTKLSHQLISDVQVLSGTIQDLQDQVD SLAEVVLQNRRLDLLTAEQGGICLALQEKCCFYANKS GIVRNKIRTLQEELQKRRESLASNPLWTGLQGFLPYLLPL LGPLLTLILLITIGPCVFNRLVQFVKDRISVVQALVLTQQ YHQLKPL
256	WPREmut1	cagtctgacgtacgcgtaatacaacctctggattacaaaattgtgaaagattgactggtattc ttaactatggtgctcctttacgctatgtggatacgctgcttaatgcctttgtatcatgctattgc ttcccgatggctttcattttctcctcctgtataaatcctgggtgctgctctttatgaggagttg tggcccggtgtcaggcaacgtggcggtggtgtgcactgtgtttgctgacgcaacccccact gggtggggcattgccaccacctgtcagctcctttccgggactttcgctttccccctcctatt gccacggcggaactcatcgccgcctgccttgcccgtgctggacaggggctcggtggtt gggcactgacaattccgtggtgtgtcggggaatcatgctcctttccttggtgctgcct gtgttgccacctggattctgcgcgggacgtccttctgctacgtcccttcggccctcaatcca gcggaccttcttcccgggcctgctgcgggctctgcggccttcccgcttctgccttc gccctcagacgagtcggatctccctttgggccgcctccccgcc
257	WPREmut2	Gagcatctaccgccattataccatattgttctgttttcttgatttgggtatacatttaaatg ttaataaaacaaaatggtggggcaatcattacatttttgggatatgtaattactagttcaggt

		gtattgccacaagacaaacttgtaagaaactttccggtatttacgctctgttctgttaatca acctctggattacaaaatttgtaaagattgactgataattcttaactttgttgctccttttacgct gtgtggatttgctgctttattgcctctgtatcttgctattgcttcccgtacggcttcgtttctcc tccttgataaatcctggttgctgtctcttttgaggagttgtggcccggtgtccgtcaacgtg gcgtggttgctctgttttgctgacgcaacccccactggctggggcattgccaccacct gtcaactcctttctgggactttcgcttccccctccgacgccacggcagaactcatcgcc gcctgccttgcccgtgctggacaggggctagggtgctgggcactgataattccgtggtg ttgtc
258	CD8 α 1	MALPVTALLLPLALLLHAARPSQFRVSPLDRTWNLGET VELKCQVLLSNPTSGCSWLFQPRGAAASPTFLLYLSQNK PKAAEGLDTQRFSGKRLGDTFVLTLSDFRRENEGYYFCS ALSNSIMYFSHFVPVFLPAKPTTTPAPRPPTPAPTIASQPL SLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGV LLLSLVITLYCNHRNRRRVCKCPRPVVKS GDKPSLSARY V
259	CD8 α 2	MALPVTALLLPLALLLHAARPSQFRVSPLDRTWNLGET VELKCQVLLSNPTSGCSWLFQPRGAAASPTFLLYLSQNK PKAAEGLDTQRFSGKRLGDTFVLTLSDFRRENEG CYFCS ALSNSIMYFSHFVPVFLPAKPTTTPAPRPPTPAPTIASQPL SLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGV LLLSLVITLYCNHRNRRRVCKCPRPVVKS GDKPSLSARY V
260	CD8 α stalk	KPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTR GLDFACD
261	CD8 α Ig-like domain-2	SQFRVSPLDRTWNLGETVELKCQVLLSNPTSGCSWLFQP RGAAASPTFLLYLSQNKPKAAEGLDTQRFSGKRLGDTF VLTLSDFRRENEG CYFCS2ALSNSIMYFSHFVPVFLPA
262	m2CD8 α	MALPVTALLLPLALLLHAARPSQFRVSPLDRTWNLGET VELKCQVLLSNPTSGCSWLFQPRGAAASPTFLLYLSQNK PKAAEGLDTQRFSGKRLGDTFVLTLSDFRRENEG CYFCS ALSNSIMYFSHFVPVFLPASVVDLPTTAQPTKKSTLKKR VCRLRPETQKGPLCSPIYIWAPLAGTCGVLLLSLVITLY CNHRNRRRVCKCPRPVVKS GDKPSLSARYV

263	MSCV promoter	Tgaaagacccacctgtaggtttggcaagctagcttaagtaacgccattttgcaaggcat ggaaaatacataactgagaatagagaagttcagatcaaggtaggaacagagacagc agaatatgggccaacaggatatctgtgtaagcagttcctgccccggctcagggccaa gaacagatgggtcccagatgcgggtccgcctcagcagtttctagagaaccatcagatgt ttccagggtgccccaaaggacctgaaaatgacctgtgccttattgaactaaccaatcagtt cgcttctcgcttctgttcgcgcgcttctgctccccgagctcaataaaagagcccacaaccc ctcact
264	WPRE	cagtctgacgtacgcgtaataacacctctggattacaaaattgtgaaagattgactggtattc ttaactatgttgccttttacgctatgtggatacgtgctttaatgcctttgtatcatgctattgc ttcccgatggctttcattttctcctctgtataaatcctggtgctgctctttatgaggagttg tggcccgtgtcaggcaacgtggcgtggtgtgcactgtgtttgctgacgcaacccccact ggttggggcattgccaccacctgtcagctcctttccgggactttcgtttccccctcctatt gccacggcggaactcatcgcgcctgccttggcgcgtgctggacaggggctcggtgtt gggcactgacaattccgtgtgtgtcggggaagctgacgtcctttccatggctgctgcgc tgtgttgcacctggattctgcgcgggacgtccttctgtacgtcccttcggccctcaatcc agcggaccttcttccgcggcctgctgccggctctgccccttctccgcgttctgcctt cgccctcagacgagtcggatctcccttgggcccgcctccccgcc
265	Furin consensus	RXXR
266	Linker	SGSG
293	CD8 β Signal peptide	MRPRLWLLAAQLTVLHGNSV
294	S19 Signal peptide	MEFGLSWLFLVAILKGVQC
303	R11P3D3KE beta chain	MDSWTFCCVSLCILVAKHTDAGVIQSPRHEVTEMGQEV TLRCKPISGHNSLFWYRETMMRGLELLIYFNNNPIDDS GMPEDRFS AKMPNASFSTLKIQPSEPRDSAVYFCASSPGS TDTQYFGPGTRLTVLEDLKNVFPPEVAVFEPSEAEISHTQ KATLVCLATGFYPDHVELSWWVNGKEVHSGVSTDPQP LKEQPALNDSRYCLSSRLRVSAFWQNPRNHFRCQVQF YGLSENDEWTQDRAKPVTQIVSAEAWGRADCGFTSESY QQGVLSATILYEILLGKATLYAVLVSAVLMLAMVVKRKD SRG
304	R39P1C12 alpha chain	MKTFAGFSFLFLWLQLDCMSRGEDVEQSLFLSVREGDSS VINCTYTDSSSTLYWYKQEPGAGLQLLTYIFSNMDMK

		QDQRLTVLLNKKDKHLSLRIADTQTGDSAIYFCAEIDNQ GGKLIFGQGTLSVKPNIQNPDPVYQLRDSKSSDKSVC LFTDFDSQTNVSQSKDSDVYITDKTVLDMRSMDFKSNS AVAWSNKSDFACANAFNNSIIPEDTFFPSPESSCDVKLVE KSFETDTNLFQNLVIGFRILLKLVAGFNLLMTLRLWSS
305	Full Wild Type IL-15 (“wtIL- 15”) Amino Acid Sequence	MRISKPHLRSISIQCYLCLLNSHFLTEAGIHVFILGCFS GLPKTEANWVNVISDLKKIEDLIQSMHIDATLYTESDVH PSCVKVTAMKCFLELQVISLESGDASIHDTVENLILANN SLSSNGNVTESGCKECEEELEEKNIKEFLQSFVHIVQMFIN TS
306	Full Wild Type IL-15 Receptor α (“wtIL-15R α ”) Amino Acid Sequence	MAPRRARGCRTLGLPALLLLLLLRPPATRGITCPPPMSVE HADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNK ATNVAHWTTPSLKCIRDPALVHQRPAAPPSTVTTAGVTPQ PESLSPSGKEPAASSPSSNNTAATTAAIVPGSQLMPSKSPS TGTTEISSHESSHGTPSQTTAKNWELTASASHQPPGVYP QGHSDTTVAISTSTVLLCGLSAVSLACYLKSRQTPPLAS VEMEAMEALPVTWGTSSRDEDLNCSHHL
307	Mature wt IL-15 (“IL-15” or (“IL15”) Amino Acid Sequence	NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTA MKCFLELQVISLESGDASIHDTVENLILANNLSSNGN VTESGCKECEEELEEKNIKEFLQSFVHIVQMFINTS
308	Mature wt IL-15 (“IL-15” or (“IL15”) Nucleic Acid Sequence (codon optimized)	AACTGGGTGAACGTGATCTCCGACCTGAAGAAGATTG AAGATCTGATCCAGTCCATGCACATTGACGCCACCCT TTACACCGAGTCAGATGTGCATCCGAGCTGCAAGGTC ACCGCGATGAAGTGTTTCCTGCTGGAAGTCCAAGTCA TCAGCCTCGAATCCGGCGACGCTTCAATTCACGACAC TGTGGAGAACTTGATCATTCTGGCCAACAACCTCGCTG TCGTCCAATGGAAACGTGACCGAGTCCGGGTGCAAAG AGTGCGAAGAACTCGAGGAAAAGAACATCAAGGAGT TCCTGCAGTCCTTCGTGCACATCGTGCAGATGTTTATC AACACTAGC
309	Mature wt IL-15 Receptor α (“IL- 15R α ” or	ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTS SLTECVLNKATNVAHWTTPSLKCIRDPALVHQRPAAPPST VTTAGVTPQPESLSPSGKEPAASSPSSNNTAATTAAIVPG

	“IL15R α ”) Amino Acid Sequence	SQLMPSPSTGTTEISSHESSHGTPSQTTAKNWELTASA SHQPPGVYPQGHSDTTVAISTSTVLLCGLSAVSLACYL KSRQTPPLASVEMEAMEALPVTWGTSSRDEDLNCSHH L
310	Mature wt IL-15 Receptor α (“IL- 15R α ” or “IL15R α ”) Nucleic Acid Sequence	ATCACGTGCCCTCCCCCATGTCCGTGGAACACGCAG ACATCTGGGTCAAGAGCTACAGCTTGTACTCCAGGGA GCGGTACATTTGTAACCTCTGGTTTCAAGCGTAAAGCC GGCACGTCCAGCCTGACGGAGTGCGTGTTGAACAAGG CCACGAATGTCGCCCACTGGACAACCCCCAGTCTCAA ATGCATTAGAGACCCTGCCCTGGTTACCAAAGGCCA GCGCCACCCTCCACAGTAACGACGGCAGGGGTGACCC CACAGCCAGAGAGCCTCTCCCCTTCTGGAAAAGAGCC CGCAGCTTCATCTCCCAGCTCAAACAACACAGCGGCC ACAACAGCAGCTATTGTCCCGGGCTCCCAGCTGATGC CTTCAAAATCACCTTCCACAGGAACACAGAGATAAG CAGTCATGAGTCCTCCACGGCACCCCCTCTCAGACA ACAGCCAAGAACTGGGAACTCACAGCATCCGCCTCCC ACCAGCCGCCAGGTGTGTATCCACAGGGCCACAGCGA CACCAGTGTGGCTATCTCCACGTCCACTGTCCTGCTGT GTGGGCTGAGCGCTGTGTCTCTCCTGGCATGCTACCTC AAGTCAAGGCAAACCTCCCCGCTGGCCAGCGTTGAAA TGGAAGCCATGGAGGCTCTGCCGGTGACTTGGGGGAC CAGCAGCAGAGATGAAGACTTGGAACCTGCTCTCAC CACCTA
311	Mature IL-15 Receptor α , with CD25 TMD (“IL15-R α TM25” or “IL15R α TM25”) Amino Acid Sequence	ITCPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTS SLTECVLNKATNVAHWTTPSLKCIRDPALVHQRPAAPPST VTTAGVTPQPESLSPSGKEPAASSPSSNNTAATTAIVPG SQLMPSPSTGTTEISSHESSHGTPSQTTAKNWELTASA SHQPPGVYPQGHSDTTVAVAGCVFLLISVLLLSGLSRQT PPLASVEMEAMEALPVTWGTSSRDEDLNCSHHL
312	Mature IL-15 Receptor α , with	ATCACGTGCCCTCCCCCATGTCCGTGGAACACGCAG ACATCTGGGTCAAGAGCTACAGCTTGTACTCCAGGGA

	CD25 TMD ("IL15-R α TM25" or "IL15R α TM25") Nucleic Acid Sequence	GCGGTACATTTGTAACCTCTGGTTTCAAGCGTAAAGCC GGCACGTCCAGCCTGACGGAGTGCGTGTTGAACAAGG CCACGAATGTCGCCCCACTGGACAACCCCCAGTCTCAA ATGCATTAGAGACCCTGCCCTGGTTCACCAAAGGCCA GCGCCACCCTCCACAGTAACGACGGCAGGGGTGACCC CACAGCCAGAGAGCCTCTCCCCTTCTGGAAAAGAGCC CGCAGCTTCATCTCCCAGCTCAAACAACACAGCGGCC ACAACAGCAGCTATTGTCCCGGGCTCCCAGCTGATGC CTTCAAAATCACCTTCCACAGGAACACAGAGATAAG CAGTCATGAGTCCTCCACGGCACCCCCTCTCAGACA ACAGCCAAGAACTGGGAACTCACAGCATCCGCCTCCC ACCAGCCGCCAGGTGTGTATCCACAGGGCCACAGCGA CACCCTGTAGCAGTGGCCGGCTGTGTTTTCTGCTGA TCAGCGTCCTCCTCCTGAGTGGGCTCTCAAGGCAAAC TCCCCCGCTGGCCAGCGTTGAAATGGAAGCCATGGAG GCTCTGCCGGTGACTTGGGGGACCAGCAGCAGAGATG AAGACTTGAAAACCTGCTCTCACCACCTA
313	Mature IL-15 Receptor α , with CD28 TMD ("IL- 15R α TM28" or "IL15R α TM28") Amino Acid Sequence	ITCPPMSVEHADIWVKSYSLSRERYICNSGFKRKAGTS SLTECVLNKATNVAHWTTPLSKCIRDPALVHQRPAAPPST VTTAGVTPQPESLSPSGKEPAASSPSSNNTAATTAIVPG SQLMPSKSPSTGTTEISSHESSHGTPSQTAKNWELTASA SHQPPGVYPQGHSDTTFWVLVVVGGVLACYSLLVTVAF IIFWVKSQRTPPLASVEMEAMEALPVTWGTSSRDEDLEN CSHHL
314	Mature IL-15 Receptor α , with CD28 TMD ("IL15-R α TM28" or "IL15R α TM28") Nucleic Acid Sequence	ATCACGTGCCCTCCCCCATGTCCGTGGAACACGCAG ACATCTGGGTCAAGAGCTACAGCTTGTAAGGGA GCGGTACATTTGTAACCTCTGGTTTCAAGCGTAAAGCC GGCACGTCCAGCCTGACGGAGTGCGTGTTGAACAAGG CCACGAATGTCGCCCCACTGGACAACCCCCAGTCTCAA ATGCATTAGAGACCCTGCCCTGGTTCACCAAAGGCCA GCGCCACCCTCCACAGTAACGACGGCAGGGGTGACCC CACAGCCAGAGAGCCTCTCCCCTTCTGGAAAAGAGCC CGCAGCTTCATCTCCCAGCTCAAACAACACAGCGGCC ACAACAGCAGCTATTGTCCCGGGCTCCCAGCTGATGC

		CTTCAAAATCACCTTCCACAGGAACCACAGAGATAAG CAGTCATGAGTCCTCCACGGCACCCCCTCTCAGACA ACAGCCAAGAACTGGGAACCTACAGCATCCGCCTCCC ACCAGCCGCCAGGTGTGTATCCACAGGGCCACAGCGA CACCACCTTTTGGGTGCTGGTGGTGGTGGTGGAGTCC TGGCTTGCTATAGCTTGCTAGTAACAGTGGCCTTTATT ATTTTCTGGGTGAAGTCAAGGCAAACCTCCCCGCTGG CCAGCGTTGAAATGGAAGCCATGGAGGCTCTGCCGGT GACTTGGGGGACCAGCAGCAGAGATGAAGACTTGGA AAACTGCTCTCACACCTA
315	Mature IL-15 Receptor α with deletion of Exon 3 ("IL- 15R Δ Ex3" or "IL15R Δ Ex3") Amino Acid Sequence	ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTS SLTECVLNKATNVAHWTPSLKCIKPAASSPSSNNTAAT TAAIVPGSQLMPSKSPSTGTTEISSHESHGTPSQTTAKN WELTASASHQPPGVYPQGHSDTTVAISTSTVLLCGLSAV SLLACYLKSRQTPPLASVEMEAMEALPVTWGTSSRDED LENCSHHL
316	Mature IL-15 Receptor α with deletion of Exon 3 ("IL- 15R Δ Ex3" or "IL15R Δ Ex3") Nucleic Acid Sequence	ATCACGTGCCCTCCCCCATGTCCGTGGAACACGCAG ACATCTGGGTCAAGAGCTACAGCTTGTA CTCCAGGGA GCGGTACATTTGTA ACTCTGGTTTCAAGCGTAAAGCC GGCACGTCCAGCCTGACGGAGTGCGTGTTGAACAAGG CCACGAATGTCGCCCCACTGGACAACCCCCAGTCTCAA ATGCATTAAGCCCGCAGCTTCATCTCCAGCTCAAAC AACACAGCGGCCACAACAGCAGCTATTGTCCCGGGCT CCCAGCTGATGCCTTCAAAATCACCTTCCACAGGAAC CACAGAGATAAGCAGTCATGAGTCCTCCACGGCACC CCCTCTCAGACAACAGCCAAGAACTGGGAACCTACAG CATCCGCCTCCCACCAGCCGCCAGGTGTGTATCCACA GGGCCACAGCGACACCACTGTGGCTATCTCCACGTCC ACTGTCCTGCTGTGTGGGCTGAGCGCTGTGTCTCTCCT GGCATGCTACCTCAAGTCAAGGCAAACCTCCCCGCTG GCCAGCGTTGAAATGGAAGCCATGGAGGCTCTGCCGG

		TGACTTGGGGGACCAGCAGCAGAGATGAAGACTTGG AAAAGTCTCTCACCACCTA
317	IL-15-L3-IL- 15R α TM25 Amino Acid Sequence	NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTA MKCFLLLELQVISLESGDASIHDTVENLILANNSLSSNGN VTESGCKECEEELEEKNIKEFLQSFVHIVQMFINTSSGGGS GGGSGGGSGGGSGGGSGGGSGGGTTLQITCPPMSVEHA DIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKAT NVAHWTTPSLKCIRDPALVHQRPPAPPSTVTTAGVTPQPE SLSPSGKEPAASSPSSNNTAATTAAIVPGSQLMPSKSPST GTTEISSHESSHGTPSQTTAKNWELTASASHQPPGVYPQ GHSDDTVAVAGCVFLLISVLLLSGLSRQTPPLASVEMEA MEALPVTWGTSSRDEDELENCSHHL
318	IL-15-L3-IL- 15R α TM25 Nucleic Acid Sequence	AACTGGGTGAACGTGATCTCCGACCTGAAGAAGATTG AAGATCTGATCCAGTCCATGCACATTGACGCCACCCT TTACACCGAGTCAGATGTGCATCCGAGCTGCAAGGTC ACCGCGATGAAGTGTTTCCTGCTGGAAGTCCAAGTCA TCAGCCTCGAATCCGGCGACGCTTCAATTCACGACAC TGTGGAGAACTTGATCATTCTGGCCAACAACCTCGCTG TCGTCCAATGGAAACGTGACCGAGTCCGGGTGCAAAG AGTGCGAAGAACTCGAGGAAAAGAACATCAAGGAGT TCCTGCAGTCCTTCGTGCACATCGTGCAGATGTTTATC AACACTAGCTCTGGTGGTGGTTCTGGTGGGGGTGGCT CTGGCGGCGGGGGATCAGGCGGAGGAGGGTCCGGAG GCGGAGGCTCTGGTGGGGGTACTCTACAGATCACGTG CCCTCCCCCATGTCCGTGGAACACGCAGACATCTGG GTCAAGAGCTACAGCTTGTACTCCAGGGAGCGGTACA TTTGTAACCTCTGGTTTCAAGCGTAAAGCCGGCACGTC CAGCCTGACGGAGTGCGTGTGAACAAGGCCACGAAT GTCGCCCCACTGGACAACCCCCAGTCTCAAATGCATTA GAGACCCTGCCCTGGTTCACCAAAGGCCAGCGCCACC CTCCACAGTAACGACGGCAGGGGTGACCCACAGCCA GAGAGCCTCTCCCTTCTGGAAAAGAGCCCGCAGCTT CATCTCCCAGCTCAAACAACACAGCGGCCACAACAGC AGCTATTGTCCCGGGCTCCAGCTGATGCCTTCAAAA

		TCACCTTCCACAGGAACACAGAGATAAGCAGTCATG AGTCCTCCCACGGCACCCCTCTCAGACAACAGCCAA GAACTGGGAACTCACAGCATCCGCCTCCCACCAGCCG CCAGGTGTGTATCCACAGGGCCACAGCGACACCACTG TAGCAGTGGCCGGCTGTGTTTTCTGCTGATCAGCGTC CTCCTCCTGAGTGGGCTCTCAAGGCAAACCCCCGC TGGCCAGCGTTGAAATGGAAGCCATGGAGGCTCTGCC GGTGACTTGGGGGACCAGCAGCAGAGATGAAGACTT GGAAAACCTGCTCTCACCACTA
319	IL-15-L1-IL- 15R α Amino Acid Sequence	NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTA MKCFLELQVISLESGDASIHDTVENLILANNSLSSNGN VTESGCKECEEELEEKNIKEFLQSFVHIVQMFINTSKESGS VSSEQLAQFRSLDITCPPPMSVEHADIWVKSYSLSYRER YICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR DPALVHQRPAAPPSTVTTAGVTPQPELSPSGKEPAASSPS SNNTAATTAAIVPGSQLMPSKSPSTGTTEISSHESSHGTPS QTTAKNWELTASASHQPPGVYPQGHSDTTVAISTSTVLL CGLSAVSLACYLKSRQTPPLASVEMEAMEALPVTWGT SSRDEDLENC SHHL
320	IL-15-L1-IL- 15R α Nucleic Acid Sequence	AACCTGGGTGAACGTGATCTCCGACCTGAAGAAGATTG AAGATCTGATCCAGTCCATGCACATTGACGCCACCCT TTACACCGAGTCAGATGTGCATCCGAGCTGCAAGGTC ACCGCGATGAAGTGTTTCCTGCTGGAACTCCAAGTCA TCAGCCTCGAATCCGGCGACGCTTCAATTCACGACAC TGTGGAGAACTTGATCATTCTGGCCAACAACCTCGCTG TCGTCCAATGGAAACGTGACCGAGTCCGGGTGCAAAG AGTGCGAAGAACTCGAGGAAAAGAACATCAAGGAGT TCCTGCAGTCCTTCGTGCACATCGTGCAGATGTTTATC AACACTAGCAAAGAGTCCGGCTCCGTGTCCTCCGAAC AGCTGGCGCAGTTTCGTTCCCTGGATATCACGTGCCCT CCCCCATGTCCGTGGAACACGCAGACATCTGGGTCA AGAGCTACAGCTTGTACTCCAGGGAGCGGTACATTTG TAACTCTGGTTTCAAGCGTAAAGCCGGCACGTCCAGC CTGACGGAGTGCGTGTTGAACAAGGCCACGAATGTCG

		CCCACTGGACAACCCCCAGTCTCAAATGCATTAGAGA CCCTGCCCTGGTTCACCAAAGGCCAGCGCCACCCTCC ACAGTAACGACGGCAGGGGTGACCCACAGCCAGAG AGCCTCTCCCCTTCTGGAAAAGAGCCCGCAGCTTCAT CTCCCAGCTCAAACAACACAGCGGCCACAACAGCAGC TATTGTCCCGGGCTCCCAGCTGATGCCTTCAAAATCAC CTCCACAGGAACCACAGAGATAAGCAGTCATGAGTC CTCCCACGGCACCCCCTCTCAGACAACAGCCAAGAAC TGGGAACTCACAGCATCCGCCTCCCACCAGCCGCCAG GTGTGTATCCACAGGGCCACAGCGACACCACTGTGGC TATCTCCACGTCCACTGTCCTGCTGTGTGGGCTGAGCG CTGTGTCTCTCCTGGCATGCTACCTCAAGTCAAGGCA AACTCCCCCGCTGGCCAGCGTTGAAATGGAAGCCATG GAGGCTCTGCCGGTGACTTGGGGGACCAGCAGCAGA GATGAAGACTTGGA AAACTGCTCTCACCACCTA
321	IL-15-L1-IL-15R α TM25 Amino Acid Sequence	NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTA MKCFLLELQVISLESGDASIHTVENLILANNSLSSNGN VTESGCKECEEELEEKNIKEFLQSFVHIVQMFINTSKESGS VSSEQLAQFRSLDITCPPPMSVEHADIWVKSYSLSYRER YICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR DPALVHQRPAAPPSTVTTAGVTPQPESLSPSGKEPAASSPS SNNTAATTAAIVPGSQLMPSKSPSTGTTEISSHESSHGTPS QTTAKNWELTASASHQPPGVYPQGHSDTTVAVAGCVFL LISVLLLSGLSRQTPPLASVEMEAMEALPVTWGTSSRDE DLENCSHHL
322	IL-15-L1-IL-15R α TM25 Nucleic Acid Sequence	AACTGGGTGAACGTGATCTCCGACCTGAAGAAGATTG AAGATCTGATCCAGTCCATGCACATTGACGCCACCCT TTACACCGAGTCAGATGTGCATCCGAGCTGCAAGGTC ACCGCGATGAAGTGTTTCCTGCTGGA ACTCCAAGTCA TCAGCCTCGAATCCGGCGACGCTTCAATTCACGACAC TGTGGAGAACTTGATCATTCTGGCCAACA ACTCGCTG TCGTCCAATGGAAACGTGACCGAGTCCGGGTGCAAAG AGTGCGAAGAACTCGAGGAAAAGAACATCAAGGAGT TCCTGCAGTCCTTCGTGCACATCGTGCAGATGTTTATC

		AACACTAGCAAAGAGTCCGGCTCCGTGTCCTCCGAAC AGCTGGCGCAGTTTCGTTCCCTGGATATCACGTGCCCT CCCCCATGTCCGTGGAACACGCAGACATCTGGGTCA AGAGCTACAGCTTGTACTCCAGGGAGCGGTACATTTG TAACTCTGGTTTCAAGCGTAAAGCCGGCACGTCCAGC CTGACGGAGTGCGTGTTGAACAAGGCCACGAATGTCG CCCACTGGACAACCCCCAGTCTCAAATGCATTAGAGA CCCTGCCCTGGTTCACCAAAGGCCAGCGCCACCCTCC ACAGTAACGACGGCAGGGGTGACCCACAGCCAGAG AGCCTCTCCCCCTTCTGGAAAAGAGCCCGCAGCTTCAT CTCCCAGCTCAAACAACACAGCGGCCACAACAGCAGC TATTGTCCCGGGCTCCCAGCTGATGCCTTCAAATCAC CTCCACAGGAACCACAGAGATAAGCAGTCATGAGTC CTCCACGGCACCCCCCTCTCAGACAACAGCCAAGAAC TGGGAACTCACAGCATCCGCCTCCCACCAGCCGCCAG GTGTGTATCCACAGGGCCACAGCGACACCACTGTAGC AGTGGCCGGCTGTGTTTTCTGCTGATCAGCGTCCTCC TCCTGAGTGGGCTCTCAAGGCAAACCTCCCCGCTGGC CAGCGTTGAAATGGAAGCCATGGAGGCTCTGCCGGTG ACTTGGGGGACCAGCAGCAGAGATGAAGACTTGGA AACTGCTCTCACCACTA
323	IL-15-L2-IL- 15R α Amino Acid Sequence	NWNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTA MKCFLLELQVISLESGDASIHDTVENLILANNSLSSNGN VTESGCKECELEEKNIKEFLQSFVHIVQMFINTSEGKSS GSGSESKSTITCPPPMSVEHADIWVKSYSLSRERYICNS GFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDPAL VHQRPAAPPSTVTTAGVTPQPESLSPSGKEPAASSPSSNNT AATTAAIVPGSQLMPSPSTGTTEISSHESHGTPSQTTA KNWELTASASHQPPGVYPQGHSDTTVAISTSTVLLCGLS AVSLLACYLKSRQTPPLASVEMEAMEALPVTWGTSSRD EDLENCSHHL
324	IL-15-L2-IL- 15R α Nucleic Acid Sequence	AACTGGGTGAACGTGATCTCCGACCTGAAGAAGATTG AAGATCTGATCCAGTCCATGCACATTGACGCCACCCT TTACACCGAGTCAGATGTGCATCCGAGCTGCAAGGTC

		ACCGCGATGAAGTGTTTCCTGCTGGAAGTCCAAGTCA TCAGCCTCGAATCCGGCGACGCTTCAATTCACGACAC TGTGGAGAACTTGATCATTCTGGCCAACAACCTCGCTG TCGTCCAATGGAAACGTGACCGAGTCCGGGTGCAAAG AGTGCGAAGAACTCGAGGAAAAGAACATCAAGGAGT TCCTGCAGTCCTTCGTGCACATCGTGCAGATGTTTATC AACACTAGCGAAGGCAAATCCTCCGGCTCCGGCTCCG AATCCAAATCCACCATCACGTGCCCTCCCCCATGTCC GTGGAACACGCAGACATCTGGGTCAAGAGCTACAGCT TGTA CTCCAGGGAGCGGTACATTTGTA ACTCTGGTTTC AAGCGTAAAGCCGGCACGTCCAGCCTGACGGAGTGC GTGTTGAACAAGGCCACGAATGTCGCCCCACTGGACAA CCCCCAGTCTCAAATGCATTAGAGACCCTGCCCTGGT TCACCAAAGGCCAGCGCCACCCTCCACAGTAACGACG GCAGGGGTGACCCACAGCCAGAGAGCCTCTCCCCTT CTGGAAAAGAGCCCGCAGCTTCATCTCCCAGCTCAAA CAACACAGCGGCCACAACAGCAGCTATTGTCCCGGGC TCCCAGCTGATGCCTTCAAATCACCTTCCACAGGAA CCACAGAGATAAGCAGTCATGAGTCCTCCACGGCAC CCCCTCTCAGACAACAGCCAAGA ACTGGGAACTCACA GCATCCGCCTCCCACCAGCCGCCAGGTGTGTATCCAC AGGGCCACAGCGACACCACTGTGGCTATCTCCACGTC CACTGTCCTGCTGTGTGGGCTGAGCGCTGTGTCTCTCC TGGCATGCTACCTCAAGTCAAGGCAA ACTCCCCGCT GGCCAGCGTTGAAATGGAAGCCATGGAGGCTCTGCCG GTGACTTGGGGGACCAGCAGCAGAGATGAAGACTTG GAAA ACTGCTCTCACCACCTA
325	IL-15-L2-IL-15R α TM25 Amino Acid Sequence	NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTA MKCFLELQVISLESGDASIHDTVENLILANNSLSSNGN VTESGCKECEEELEEKNIKEFLQSFVHIVQMFINTSEGKSS GSGSESKSTITCPPPMSVEHADIWVKSYSLYSRERYICNS GFKRKAGTSSLTECVLNKATNVAHWTPSLKCI RDPAL VHQRPA PPSTVTTAGVTPQPESLSPSGKEPAASSPSSNNT AATTAAIVPGSQLMPSPSTGTTEISSHESHGTPSQTTA

		KNWELTASASHQPPGVYPQGHSDTTVAVAGCVFLLISV LLLSGLSRQTPPLASVEMEAMEALPVTWGTSSRDEDLEN CSHHL
326	IL-15-L2-IL- 15R α TM25 Nucleic Acid Sequence	AACTGGGTGAACGTGATCTCCGACCTGAAGAAGATTG AAGATCTGATCCAGTCCATGCACATTGACGCCACCCT TTACACCGAGTCAGATGTGCATCCGAGCTGCAAGGTC ACCGCGATGAAGTGTTTCCTGCTGGAAGTCCAAGTCA TCAGCCTCGAATCCGGCGACGCTTCAATTCACGACAC TGTGGAGAACTTGATCATTCTGGCCAACAACCTCGCTG TCGTCCAATGGAAACGTGACCGAGTCCGGGTGCAAAG AGTGCGAAGAACTCGAGGAAAAGAACATCAAGGAGT TCCTGCAGTCCTTCGTGCACATCGTGCAGATGTTTATC AACACTAGCGAAGGCCAAATCCTCCGGCTCCGGCTCCG AATCCAAATCCACCATCACGTGCCCTCCCCCATGTCC GTGGAACACGCAGACATCTGGGTCAAGAGCTACAGCT TGTA CTCCAGGGAGCGGTACATTTGTA ACTCTGGTTTC AAGCGTAAAGCCGGCACGTCCAGCCTGACGGAGTGC GTGTTGAACAAGGCCACGAATGTCGCCCACTGGACAA CCCCCAGTCTCAAATGCATTAGAGACCCTGCCCTGGT TCACCAAAGGCCAGCGCCACCCTCCACAGTAACGACG GCAGGGGTGACCCACAGCCAGAGAGCCTCTCCCCTT CTGGAAAAGAGCCCGCAGCTTCATCTCCAGCTCAAA CAACACAGCGGCCACAACAGCAGCTATTGTCCCGGGC TCCCAGCTGATGCCTTCAAAATCACCTTCCACAGGAA CCACAGAGATAAGCAGTCATGAGTCCTCCACGGCAC CCCCTCTCAGACAACAGCCAAGAACTGGGAACTCACA GCATCCGCCTCCCACCAGCCGCCAGGTGTGTATCCAC AGGGCCACAGCGACACCACTGTAGCAGTGGCCGGCTG TGTTTTCTGCTGATCAGCGTCCTCCTCCTGAGTGGGC TCTCAAGGCAAACCTCCCCCGCTGGCCAGCGTTGAAAT GGAAGCCATGGAGGCTCTGCCGGTGACTTGGGGGACC AGCAGCAGAGATGAAGACTTGGAAAACCTGCTCTCACC ACCTA

327	IL-15-L4-IL-15R α TM25 Amino Acid Sequence	NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTA MKCFLLELQVISLESGDASIHDTVENLILANNSLSSNGN VTESGCKECEEELEEKNIKEFLQSFVHIVQMFINTSSGGGS GGGSGGGSGGGTTLQITCPPMSVEHADIWVKSYSLY SRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSL KCIRDPALVHQRPPAPPSTVTTAGVTPQPESLSPSGKEPAA SSPSSNNTAATTAAIVPGSQLMPSKSPSTGTTEISSHESH GTPSQTTAKNWELTASASHQPPGVYPQGHSDTTVAVAG CVFLLISVLLLSGLSRQTPPLASVEMEAMEALPVTWGTS SRDEDLENCSHHL
328	IL-15-L4-IL-15R α TM25 Nucleic Acid Sequence	AACTGGGTGAACGTGATCTCCGACCTGAAGAAGATTG AAGATCTGATCCAGTCCATGCACATTGACGCCACCCT TTACACCGAGTCAGATGTGCATCCGAGCTGCAAGGTC ACCGCGATGAAGTGTTTCCTGCTGGAAGTCCAAGTCA TCAGCCTCGAATCCGGCGACGCTTCAATTCACGACAC TGTGGAGAACTTGATCATTCTGGCCAACAACCTCGCTG TCGTCCAATGGAAACGTGACCGAGTCCGGGTGCAAAG AGTGCGAAGAACTCGAGGAAAAGAACATCAAGGAGT TCCTGCAGTCCTTCGTGCACATCGTGCAGATGTTTATC AACACTAGCTCTGGTGGTGGTTCTGGTGGGGGTGGCT CTGGCGGCGGGGGATCTGGTGGGGGTACTCTACAGAT CACGTGCCCTCCCCCATGTCCGTGGAACACGCAGAC ATCTGGGTCAAGAGCTACAGCTTGACTCCAGGGAGC GGTACATTTGTAACCTCTGGTTTCAAGCGTAAAGCCGG CACGTCCAGCCTGACGGAGTGCGTGTTGAACAAGGCC ACGAATGTCGCCCCTGGACAACCCCCAGTCTCAAAT GCATTAGAGACCCTGCCCTGGTTCACCAAAGGCCAGC GCCACCCTCCACAGTAACGACGGCAGGGGTGACCCCA CAGCCAGAGAGCCTCTCCCCTTCTGGAAAAGAGCCCG CAGCTTCATCTCCCAGCTCAAACAACACAGCGGCCAC AACAGCAGCTATTGTCCCGGGCTCCCAGCTGATGCCT TCAAATCACCTTCCACAGGAACCACAGAGATAAGCA GTCATGAGTCCTCCACGGCACCCCCTCTCAGACAAC AGCCAAGAACTGGGAACTCACAGCATCCGCCTCCCAC

		CAGCCGCCAGGTGTGTATCCACAGGGCCACAGCGACA CCACTGTAGCAGTGGCCGGCTGTGTTTTCTGTCTGATC AGCGTCCTCCTCCTGAGTGGGCTCTCAAGGCAAATC CCCCGCTGGCCAGCGTTGAAATGGAAGCCATGGAGGC TCTGCCGGTGACTTGGGGGACCAGCAGCAGAGATGAA GACTTGGA AAACTGCTCTCACCACCTA
329	IL-15-L3-IL- 15R α TM28 Amino Acid Sequence	NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTA MKCFLELQVISLESGDASIHDTVENLIILANNSLSSNGN VTESGCKECEEELEEKNIKEFLQSFVHIVQMFINTSSGGGS GGGSGGGSGGGSGGGSGGGSGGGTTLQITCPPPMSVEHA DIWVKSYSLSYRERYICNSGFKRKAGTSSLTECVLNKAT NVAHWTTPSLKCIRD PALVHQR PAPPSTVTTAGVTPQPE SLSPSGKEPAASSPSSNNTAATTAAIVPGSQLMPSPST GTTEISSHESHGTPSQTAKNWELTASASHQPPGVYPQ GHSDTTFWVLVVVGGVLACYSLLVTVAFIIFWVKS RQT PPLASVEMEAMEALPVTWGTSSRDEDLENC SHHL
330	IL-15-L3-IL- 15R α TM28 Nucleic Acid Sequence	AACTGGGTGAACGTGATCTCCGACCTGAAGAAGATTG AAGATCTGATCCAGTCCATGCACATTGACGCCACCCT TTACACCGAGTCAGATGTGCATCCGAGCTGCAAGGTC ACCGCGATGAAGTGTTCCTGCTGGA ACTCCAAGTCA TCAGCCTCGAATCCGGCGACGCTTCAATTCACGACAC TGTGGAGAACTTGATCATTCTGGCCAACA ACTCGCTG TCGTCCAATGGAAACGTGACCGAGTCCGGGTGCAAAG AGTGCGAAGAACTCGAGGAAAAGAACATCAAGGAGT TCCTGCAGTCCTTCGTGCACATCGTGCAGATGTTTATC AACACTAGCTCTGGTGGTGGTTCTGGTGGGGGTGGCT CTGGCGGCGGGGGATCAGGCGGAGGAGGGTCCGGAG GCGGAGGCTCTGGTGGGGGTACTCTACAGATCACGTG CCCTCCCCCATGTCCGTGGAACACGCAGACATCTGG GTCAAGAGCTACAGCTTG TACTCCAGGGAGCGGTACA TTTGTA ACTCTGGTTTCAAGCGTAAAGCCGGCACGTC CAGCCTGACGGAGTGC GTTTGAACAAGGCCACGAAT GTCGCCCACTGGACAACCCCCAGTCTCAAATGCATTA GAGACCCTGCCCTGGTTCACCAAAGGCCAGCGCCACC

		CTCCACAGTAACGACGGCAGGGGTGACCCACAGCCA GAGAGCCTCTCCCCTTCTGGAAAAGAGCCCGCAGCTT CATCTCCCAGCTCAAACAACACAGCGGCCACAACAGC AGCTATTGTCCCGGGCTCCCAGCTGATGCCTTCAAAA TCACCTTCCACAGGAACCACAGAGATAAGCAGTCATG AGTCCTCCCACGGCACCCCTCTCAGACAACAGCCAA GAACTGGGAACCTCACAGCATCCGCCTCCCACCAGCCG CCAGGTGTGTATCCACAGGGCCACAGCGACACCACTT TTTGGGTGCTGGTGGTGGTTGGTGGAGTCCTGGCTTGC TATAGCTTGCTAGTAACAGTGGCCTTTATTATTTTCTG GGTGAAGTCAAGGCAAACTCCCCCGCTGGCCAGCGTT GAAATGGAAGCCATGGAGGCTCTGCCGGTGACTTGGG GGACCAGCAGCAGAGATGAAGACTTGAAAACTGCT CTCACCACCTA
331	IL-15-L1-IL- 15RadEx3 Amino Acid Sequence	NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTA MKCFLELQVISLESGDASIHTVENLILANNSLSSNGN VTESGCKECEEELEEKNIKEFLQSFVHIVQMFINTSKESGS VSSEQLAQFRSLDITCPPPMSVEHADIWVKSYSLYSRER YICNSGFKRKAGTSSLTECVLNKATNVAHWTTPLSKCIK PAASSPSSNNTAATTAIVPGSQLMPSPSTGTTEISSHE SSHGTPSQTTAKNWELTASASHQPPGVYPQGHSDTTVAI STSTVLLCGLSAVSLACYLKSRQTPPLASVEMEAMEAL PVTWGTSSRDEDLNCSHHL
332	IL-15-L1-IL- 15RadEx3 Nucleic Acid Sequence	AACTGGGTGAACGTGATCTCCGACCTGAAGAAGATTG AAGATCTGATCCAGTCCATGCACATTGACGCCACCCT TTACACCGAGTCAGATGTGCATCCGAGCTGCAAGGTC ACCGCGATGAAGTGTTTCCTGCTGGAAGTCCAAGTCA TCAGCCTCGAATCCGGCGACGCTTCAATTCACGACAC TGTGGAGAACTTGATCATTCTGGCCAACAACCTCGCTG TCGTCCAATGGAAACGTGACCGAGTCCGGGTGCAAAG AGTGCGAAGAACTCGAGGAAAAGAACATCAAGGAGT TCCTGCAGTCCTTCGTGCACATCGTGCAGATGTTTATC AACACTAGCAAAGAGTCCGGCTCCGTGTCCTCCGAAC AGCTGGCGCAGTTTCGTTCCCTGGATATCACGTGCCCT

		CCCCCATGTCCGTGGAACACGCAGACATCTGGGTCA AGAGCTACAGCTTGTACTCCAGGGAGCGGTACATTTG TAACTCTGGTTTCAAGCGTAAAGCCGGCACGTCCAGC CTGACGGAGTGCGTGTGTAACAAGGCCACGAATGTCTG CCCACTGGACAACCCCCAGTCTCAAATGCATTAAGCC CGCAGCTTCATCTCCCAGCTCAAACAACACAGCGGCC ACAACAGCAGCTATTGTCCCGGGCTCCCAGCTGATGC CTTCAAAATCACCTTCCACAGGAACCACAGAGATAAG CAGTCATGAGTCCTCCACGGCACCCCCTCTCAGACA ACAGCCAAGAACTGGGAACTCACAGCATCCGCCTCCC ACCAGCCGCCAGGTGTGTATCCACAGGGCCACAGCGA CACCCTGTGGCTATCTCCACGTCCACTGTCCTGCTGT GTGGGCTGAGCGCTGTGTCTCTCCTGGCATGCTACCTC AAGTCAAGGCAAACCTCCCCCGCTGGCCAGCGTTGAAA TGGAAGCCATGGAGGCTCTGCCGGTGACTTGGGGGAC CAGCAGCAGAGATGAAGACTTGGAAGAACTGCTCTCAC CACCTA
333	IL-15-L2-IL- 15RadEx3 Amino Acid Sequence	NWNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTA MKCFLELQVISLESGDASIHTVENLILANNSLSSNGN VTESGCKECEEELEEKNIKEFLQSFVHIVQMFINTSEGKSS GSGSESKSTITCPPPMSVEHADIWVKSYSLYSRERYICNS GFKRKAGTSSLTECVLNKATNVAHWTPSLKCIKPAASS PSSNNTAATTAIVPGSQLMPSKSPSTGTTEISSHESHGT PSQTTAKNWELTASASHQPPGVYPQGHSDTTVAISTSTV LLCGLSAVSLLACYLKSRTPLASVEMEAMEALPVTW GTSSRDEDELENCSHHL
334	IL-15-L2-IL- 15RadEx3 Nucleic Acid Sequence	AACTGGGTGAACGTGATCTCCGACCTGAAGAAGATTG AAGATCTGATCCAGTCCATGCACATTGACGCCACCCT TTACACCGAGTCAGATGTGCATCCGAGCTGCAAGGTC ACCGCGATGAAGTGTTTCCTGCTGGAAGTCCAAGTCA TCAGCCTCGAATCCGGCGACGCTTCAATTCACGACAC TGTGGAGAACTTGATCATTCTGGCCAACAACCTCGCTG TCGTCCAATGGAAACGTGACCGAGTCCGGGTGCAAAG AGTGCGAAGAACTCGAGGAAAAGAACATCAAGGAGT

		TCCTGCAGTCCTTCGTGCACATCGTGCAGATGTTTATC AACACTAGCGAAGGCCAAATCCTCCGGCTCCGGCTCCG AATCCAAATCCACCATCACGTGCCCTCCCCCATGTCC GTGGAACACGCAGACATCTGGGTCAAGAGCTACAGCT TGTA CTCCAGGGAGCGGTACATTTGTA ACTCTGGTTTC AAGCGTAAAGCCGGCACGTCCAGCCTGACGGAGTGC GTGTTGAACAAGGCCACGAATGTCGCCCACTGGACAA CCCCAGTCTCAAATGCATTAAGCCCGCAGCTTCATCT CCCAGCTCAAACAACACAGCGGCCACAACAGCAGCT ATTGTCCCGGGCTCCCAGCTGATGCCTTCAAAATCAC CTCCACAGGAACCACAGAGATAAGCAGTCATGAGTC CTCCACGGCACCCCTCTCAGACAACAGCCAAGAAC TGGGAACTCACAGCATCCGCCTCCCACCAGCCGCCAG GTGTGTATCCACAGGGCCACAGCGACCACTGTGGC TATCTCCACGTCCACTGTCCTGCTGTGTGGGCTGAGCG CTGTGTCTCTCCTGGCATGCTACCTCAAGTCAAGGCA AACTCCCCCGCTGGCCAGCGTTGAAATGGAAGCCATG GAGGCTCTGCCGGTGACTTGGGGGACCAGCAGCAGA GATGAAGACTTGGA AAACTGCTCTCACCACCTA
335	IL-15-L5-IL- 15R α Amino Acid Sequence	NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTA MKCFLELQVISLESGDASIHTVENLILANNSLSSNGN VTESGCKECELEEKNIKEFLQSFVHIVQMFINTSSGGGS GGGGSGGGSGGGSGGGSLQITCPPPMSVEHADIWVK SYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAH WTPSLKCIRD PALVHQR PAPPSTVTTAGVTPQESLSPS GKEPAASSPSSNNTAATTAAIVPGSQLMP SKSPSTGTTEI SSHESHGTPSQTTAKNWELTASASHQPPGVYPQGHSDT TVAISTSTVLLCGLSAVSLLACYLKS RQTPPLASVEMEA MEALPVTWGTSSRDEDL ENC SHHL
336	IL-15-L5-IL- 15R α Nucleic Acid Sequence	AACTGGGTGAACGTGATCTCCGACCTGAAGAAGATTG AAGATCTGATCCAGTCCATGCACATTGACGCCACCCT TTACACCGAGTCAGATGTGCATCCGAGCTGCAAGGTC ACCGCGATGAAGTGTTTCCTGCTGGA ACTCCAAGTCA TCAGCCTCGAATCCGGCGACGCTTCAATTCACGACAC

		TGTGGAGAACTTGATCATTCTGGCCAACAACCTCGCTG TCGTCCAATGGAAACGTGACCGAGTCCGGGTGCAAAG AGTGCGAAGAACTCGAGGAAAAGAACATCAAGGAGT TCCTGCAGTCCTTCGTGCACATCGTGCAGATGTTTATC AACACTAGCAGCGGCGGCGGCAGCGGCGGCGGCGGC AGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGC GGCGGCAGCCTACAGATCACGTGCCCTCCCCCATGT CCGTGGAACACGCAGACATCTGGGTCAAGAGCTACAG CTTGTACTCCAGGGAGCGGTACATTTGTAACCTCTGGTT TCAAGCGTAAAGCCGGCACGTCCAGCCTGACGGAGTG CGTGTTGAACAAGGCCACGAATGTCGCCCACTGGACA ACCCCCAGTCTCAAATGCATTAGAGACCCTGCCCTGG TTCACCAAAGGCCAGCGCCACCCTCCACAGTAACGAC GGCAGGGGTGACCCACAGCCAGAGAGCCTCTCCCCT TCTGGAAAAGAGCCCGCAGCTTCATCTCCCAGCTCAA ACAACACAGCGGCCACAACAGCAGCTATTGTCCCGGG CTCCCAGCTGATGCCTTCAAATCACCTTCCACAGGA ACCACAGAGATAAGCAGTCATGAGTCCTCCACGGCA CCCCCTCTCAGACAACAGCCAAGAACTGGGAACTCAC AGCATCCGCCTCCCACCAGCCGCCAGGTGTGTATCCA CAGGGCCACAGCGACACCACTGTGGCTATCTCCACGT CCACTGTCCTGCTGTGTGGGCTGAGCGCTGTGTCTCTC CTGGCATGCTACCTCAAGTCAAGGCAAACCTCCCCGC TGGCCAGCGTTGAAATGGAAGCCATGGAGGCTCTGCC GGTGACTTGGGGGACCAGCAGCAGAGATGAAGACTT GGAAAACCTGCTCTCACCACCTA
337	IgESP-IL-15-L3- IL-15RαTM25 Amino Acid Sequence	MDWTWILFLVAAATRVHSNWVNVISDLKKIEDLIQSMH IDATLYTESDVHPSCCKVTAMKCFLELQVISLESGDASIH DTVENLILANNSLSSNGNVTESGCKECELEEKNIKEFL QSFVHIVQMFINTSSGGGSGGGGSGGGGSGGGGSGGGG SGGGTLQITCPPPMSVEHADIWVKSYSLSYRERYICNSGF KRKAGTSSLTECVLNKATNVAHWTPSLKCI RDPALVH QRPAPPSTVTTAGVTPQPESLSPSGKEPAASSPSSNNTAA TTAAIVPGSQLMPSPSTGTTEISSHESHGTPSQTTAKN

		WELTASASHQPPGVYPQGHSDTTVAVAGCVFLLISVLLL SGLSRQTPPLASVEMEAMEALPVTWGTSSRDELENC HHL
338	IgESP-IL-15-L3- IL-15R α TM25 Nucleic Acid Sequence	ATGGACTGGACCTGGATCCTCTTCTTGGTGGCAGCAG CCACGCGAGTCCACTCCAAGTGGGTGAACGTGATCTC CGACCTGAAGAAGATTGAAGATCTGATCCAGTCCATG CACATTGACGCCACCCTTTACACCGAGTCAGATGTGC ATCCGAGCTGCAAGGTCACCGCGATGAAGTGTTTCCT GCTGGAAGTCCAAGTCATCAGCCTCGAATCCGGCGAC GCTTCAATTACAGACACTGTGGAGAACTTGATCATTCT GGCCAACAAGTTCGCTGTCGTCCAATGGAAACGTGACC GAGTCCGGGTGCAAAGAGTGCGAAGAACTCGAGGAA AAGAACATCAAGGAGTTCCTGCAGTCCTTCGTGCACA TCGTGCAGATGTTTATCAACACTAGCTCTGGTGGTGGT TCTGGTGGGGGTGGCTCTGGCGGCGGGGGATCAGGCG GAGGAGGGTCCGGAGGCGGAGGCTCTGGTGGGGGTA CTCTACAGATCACGTGCCCTCCCCCATGTCCGTGGA ACACGCAGACATCTGGGTCAAGAGCTACAGCTTGTA TCCAGGGAGCGGTACATTTGTAAGTCTGGTTTCAAGC GTAAAGCCGGCACGTCCAGCCTGACGGAGTGCGTGTT GAACAAGGCCACGAATGTCGCCCCTGGACAACCCCC AGTCTCAAATGCATTAGAGACCCTGCCCTGGTTTACC AAAGGCCAGCGCCACCCTCCACAGTAACGACGGCAG GGGTGACCCACAGCCAGAGAGCCTCTCCCCTTCTGG AAAAGAGCCCGCAGCTTCATCTCCAGCTCAAACAAC ACAGCGGCCACAACAGCAGCTATTGTCCCGGGCTCCC AGCTGATGCCTTCAAAATCACCTTCCACAGGAACCAC AGAGATAAGCAGTCATGAGTCCTCCACGGCACCCCC TCTCAGACAACAGCCAAGAACTGGGAACTCACAGCAT CCGCCTCCCACCAGCCGCCAGGTGTGTATCCACAGGG CCACAGCGACACCACTGTAGCAGTGGCCGGCTGTGTT TTCCTGCTGATCAGCGTCCTCCTCCTGAGTGGGCTCTC AAGGCAAAGTCCCCCGCTGGCCAGCGTTGAAATGGAA GCCATGGAGGCTCTGCCGGTGACTTGGGGGACCAGCA

		GCAGAGATGAAGACTTGGA AAACTGCTCTCACCACCT A
339	IgESP-IL-15-L1- IL-15R α Amino Acid Sequence	MDWTWILFLVAAATRVHSNWVNVISDLKKIEDLIQSMH IDATLYTESDVHPSCKVTAMKCFLELQVISLESGDASIH DTVENLILANNSLSSNGNVTESGCKECEEELEEKNIKEFL QSFVHIVQMFINTSKESGSVSSEQLAQFRSLDITCPPPMS VEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVL NKATNVAHWTTPSLKCIRD PALVHQR PAPPSTVTTAGV TPQPESLSPSGKEPAASSPSSNNTAATTAAIVPGSQLMPS KSPSTGTTEISSHESHGTPSQTTAKNWELTASASHQPPG VYPQGHSDTTVAISTSTVLLCGLSAVSLLACYLKS RQTPP LASVEMEAMEALPVTWGTSSRDELENC SHHL
340	IgESP-IL-15-L1- IL-15R α Nucleic Acid Sequence	ATGGACTGGACCTGGATCCTCTTCTTGGTGGCAGCAG CCACGCGAGTCCACTCCA ACTGGGTGAACGTGATCTC CGACCTGAAGAAGATTGAAGATCTGATCCAGTCCATG CACATTGACGCCACCCTTTACACCGAGTCAGATGTGC ATCCGAGCTGCAAGGTCACCGCGATGAAGTGTTTCCT GCTGGA ACTCCAAGTCATCAGCCTCGAATCCGGCGAC GCTTCAATTACGACACTGTGGAGAACTTGATCATTCT GGCCAACA ACTCGCTGTCGTCCAATGGAAACGTGACC GAGTCCGGGTGCAAAGAGTGCGAAGAACTCGAGGAA AAGAACATCAAGGAGTTCCTGCAGTCCTTCGTGCACA TCGTGCAGATGTTTATCAACACTAGCAAAGAGTCCGG CTCCGTGTCCTCCGAACAGCTGGCGCAGTTTCGTTCCC TGGATATCACGTGCCCTCCCCCATGTCCGTGGAACA CGCAGACATCTGGGTCAAGAGCTACAGCTTG TACTCC AGGGAGCGGTACATTTGTA ACTCTGGTTTCAAGCGTA AAGCCGGCAGTCCAGCCTGACGGAGTGCGTGTTGAA CAAGGCCACGAATGTCGCCC ACTGGACAACCCCCAGT CTCAAATGCATTAGAGACCCTGCCCTGGTTACCAAAA GGCCAGCGCCACCCTCCACAGTAACGACGGCAGGGGT GACCCACAGCCAGAGAGCCTCTCCCCTTCTGGAAAA GAGCCCGCAGCTTCATCTCCAGCTCAAACAACACAG CGGCCACAACAGCAGCTATTGTCCCGGGCTCCAGCT

		GATGCCTTCAAAATCACCTTCCACAGGAACACAGAG ATAAGCAGTCATGAGTCCTCCACGGCACCCCCTCTC AGACAACAGCCAAGAACTGGGAACACAGCATCCG CCTCCCACCAGCCGCCAGGTGTGTATCCACAGGGCCA CAGCGACACCACTGTGGCTATCTCCACGTCCACTGTC CTGCTGTGTGGGCTGAGCGCTGTGTCTCTCCTGGCATG CTACCTCAAGTCAAGGCAAACCTCCCCGCTGGCCAGC GTTGAAATGGAAGCCATGGAGGCTCTGCCGGTGACTT GGGGGACCAGCAGCAGAGATGAAGACTTGAAAACT GCTCTCACCACCTA
341	IgESP-IL-15-L1- IL-15R α TM25 Amino Acid Sequence	MDWTWILFLVAAATRVHSNWVNVISDLKKIEDLIQSMH IDATLYTESDVHPSCKVTAMKCFLELQVISLESGDASIH DTVENLILANNSLSSNGNVTESGCKECEEELEEKNIKEFL QSFVHIVQMFINTSKESGSVSSEQLAQFRSLDITCPPPMS VEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVL NKATNVAHWTTTPSLKCIRDPALVHQRPAAPPSTVTTAGV TPQPESLSPSGKEPAASSPSSNNTAATTAAIVPGSQLMPS KSPSTGTTEISSHESHGTPSQTTAKNWELTASASHQPPG VYPQGHSDTTVAVAGCVFLLISVLLLSGLSRQTPPLASV EMEAMEALPVTWGTSSRDELENC SHHL
342	IgESP-IL-15-L1- IL-15R α TM25 Nucleic Acid Sequence	ATGGACTGGACCTGGATCCTCTTCTTGGTGGCAGCAG CCACGCGAGTCCACTCCAACCTGGGTGAACGTGATCTC CGACCTGAAGAAGATTGAAGATCTGATCCAGTCCATG CACATTGACGCCACCCTTTACACCGAGTCAGATGTGC ATCCGAGCTGCAAGGTCACCGCGATGAAGTGTTTCCT GCTGGAACCTCCAAGTCATCAGCCTCGAATCCGGCGAC GCTTCAATTACGACACTGTGGAGAACTTGATCATTCT GGCCAACAACCTCGCTGTCGTCCAATGGAAACGTGACC GAGTCCGGGTGCAAAGAGTGCGAAGAACTCGAGGAA AAGAACATCAAGGAGTTCCTGCAGTCCTTCGTGCACA TCGTGCAGATGTTTATCAACACTAGCAAAGAGTCCGG CTCCGTGTCCTCCGAACAGCTGGCGCAGTTTCGTTCCC TGGATATCACGTGCCCTCCCCCATGTCCGTGGAACA CGCAGACATCTGGGTCAAGAGCTACAGCTTG TACTCC

		AGGGAGCGGTACATTTGTA ACTCTGGTTTCAAGCGTA AAGCCGGCACGTCCAGCCTGACGGAGTGC GTGTTGAA CAAGGCCACGAATGTCGCCCCACTGGACAACCCCCAGT CTCAAATGCATTAGAGACCCTGCCCTGGTTCACCAAA GGCCAGCGCCACCCTCCACAGTAACGACGGCAGGGGT GACCCACAGCCAGAGAGCCTCTCCCCTTCTGGAAAA GAGCCCGCAGCTTCATCTCCCAGCTCAAACAACACAG CGGCCACAACAGCAGCTATTGTCCCGGGCTCCAGCT GATGCCTTCAAATCACCTTCCACAGGAACCACAGAG ATAAGCAGTCATGAGTCCTCCACGGCACCCCCTCTC AGACAACAGCCAAGAACTGGGAACTCACAGCATCCG CCTCCCACCAGCCGCCAGGTGTGTATCCACAGGGCCA CAGCGACACCACTGTAGCAGTGGCCGGCTGTGTTTTC CTGCTGATCAGCGTCCTCCTCCTGAGTGGGCTCTCAAG GCAAAC TCCCCCGCTGGCCAGCGTTGAAATGGAAGCC ATGGAGGCTCTGCCGGTGACTTGGGGGACCAGCAGCA GAGATGAAGACTTGGA AAACTGCTCTCACCACCTA
343	IgESP-IL-15-L2- IL-15R α Amino Acid Sequence	MDWTWILFLVAAATRVHSNWVNVISDLKKIEDLIQSMH IDATLYTESDVHPSCKVTAMKCFLELQVISLESGDASIH DTVENLILANNSLSSNGNVTESGCKECELEEKNIKEFL QSFVHIVQMFINTSEGKSSGSGSESKSTITCPPPM SVEHA DIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKAT NVAHWTTPSLKCIRD PALVHQR PAPPSTVTTAGVTPQPE SLSPSGKEPAASSPSSNNTAATTAAIVPGSQLMPSKSPST GTTEISSHESHGTPSQTTAKNWELTASASHQPPGVYPQ GHS DTTVAISTSTVLLCGLSAV SLLACYLKS RQTPPLASV EMEAMEALPVTWGTSSRDEDL ENCSHHL
344	IgESP-IL-15-L2- IL-15R α Nucleic Acid Sequence	ATGGACTGGACCTGGATCCTCTTCTTGGTGGCAGCAG CCACGCGAGTCCACTCCA ACTGGGTGAACGTGATCTC CGACCTGAAGAAGATTGAAGATCTGATCCAGTCCATG CACATTGACGCCACCCTTTACACCGAGTCAGATGTGC ATCCGAGCTGCAAGGTCACCGCGATGAAGTGTTTCCT GCTGGA ACTCCAAGTCATCAGCCTCGAATCCGGCGAC GCTTCAATTCACGACACTGTGGAGAACTTGATCATTCT

		GGCCAACAACCTCGCTGTCGTCCAATGGAAACGTGACC GAGTCCGGGTGCAAAGAGTGCGAAGAACTCGAGGAA AAGAACATCAAGGAGTTCCTGCAGTCCTTCGTGCACA TCGTGCAGATGTTTATCAACACTAGCGAAGGCAAATC CTCCGGCTCCGGCTCCGAATCCAAATCCACCATCACG TGCCCTCCCCCATGTCCGTGGAACACGCAGACATCT GGGTCAAGAGCTACAGCTTGTACTCCAGGGAGCGGTA CATTTGTAACCTCTGGTTTCAAGCGTAAAGCCGGCACG TCCAGCCTGACGGAGTGCGTGTTGAACAAGGCCACGA ATGTCGCCCCACTGGACAACCCCCAGTCTCAAATGCAT TAGAGACCCTGCCCTGGTTCACCAAAGGCCAGCGCCA CCCTCCACAGTAACGACGGCAGGGGTGACCCACAGC CAGAGAGCCTCTCCCCTTCTTGAAAAGAGCCCGCAGC TTCATCTCCCAGCTCAAACAACACAGCGGCCACAACA GCAGCTATTGTCCCGGGCTCCCAGCTGATGCCTTCAA AATCACCTTCCACAGGAACACAGAGATAAGCAGTCA TGAGTCCTCCCACGGCACCCCCTCTCAGACAACAGCC AAGAACTGGGAACTCACAGCATCCGCTCCACCAGC CGCCAGGTGTGTATCCACAGGGCCACAGCGACACCAC TGTGGCTATCTCCACGTCCACTGTCCTGCTGTGTGGGC TGAGCGCTGTGTCTCTCCTGGCATGCTACCTCAAGTCA AGGCAAACCTCCCCGCTGGCCAGCGTTGAAATGGAAG CCATGGAGGCTCTGCCGGTGACTTGGGGGACCAGCAG CAGAGATGAAGACTTGGAACCTGCTCTCACCACCTA
345	IgESP-IL-15-L2- IL-15R α TM25 Amino Acid Sequence	MDWTWILFLVAAATRVHSNWVNVISDLKKIEDLIQSMH IDATLYTESDVHPSCKV TAMKCFLELQVISLESGDASIH DTVENLILANNSLSSNGNVTESGCKECELEEKNIKEFL QSFVHIVQMFINTSEGKSSGSGSESKSTITCPPPMSVEHA DIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKAT NVAHWTTPSLKCIRD PALVHQR PAPPSTVTTAGVTPQPE SLSPSGKEPAASSPSSNNTAATTAIVPGSQLMPSKSPST GTTEISSHESSHGTPSQTAKNWELTASASHQPPGVYPQ GHSDDTVAVAGCVLLISVLLLSGLSRQTPPLASVEMEA MEALPVTWGTSSRDEDLNCSHHL

346	IgESP-IL-15-L2- IL-15R α TM25 Nucleic Acid Sequence	ATGGACTGGACCTGGATCCTCTTCTTGGTGGCAGCAG CCACGCGAGTCCACTCCAAGTGGGTGAACGTGATCTC CGACCTGAAGAAGATTGAAGATCTGATCCAGTCCATG CACATTGACGCCACCCTTTACACCGAGTCAGATGTGC ATCCGAGCTGCAAGGTCACCGCGATGAAGTGTTCCT GCTGGAAGTCCAAGTCATCAGCCTCGAATCCGGCGAC GCTTCAATTACGACACTGTGGAGAACTTGATCATTCT GGCCAACAAGTCCGCTGTCGTCCAATGGAAACGTGACC GAGTCCGGGTGCAAAGAGTGCGAAGAACTCGAGGAA AAGAACATCAAGGAGTTCCTGCAGTCCTTCGTGCACA TCGTGCAGATGTTTATCAACACTAGCGAAGGCAAATC CTCCGGCTCCGGCTCCGAATCCAAATCCACCATCACG TGCCCTCCCCCATGTCCGTGGAACACGCAGACATCT GGGTCAAGAGCTACAGCTTGTACTCCAGGGAGCGGTA CATTTGTAAGTCTGGTTTCAAGCGTAAAGCCGGCACG TCCAGCCTGACGGAGTGCGTGTTGAACAAGGCCACGA ATGTCGCCCAGTGGACAACCCCCAGTCTCAAATGCAT TAGAGACCCTGCCCTGGTTACCAAAGGCCAGCGCCA CCCTCCACAGTAACGACGGCAGGGGTGACCCACAGC CAGAGAGCCTCTCCCCTTCTGGAAGAGCCCGCAGC TTCATCTCCCAGCTCAAACAACACAGCGGCCACAACA GCAGCTATTGTCCCGGGCTCCAGCTGATGCCTTCAA AATCACCTTCCACAGGAACACAGAGATAAGCAGTCA TGAGTCCTCCACGGCACCCCCTCTCAGACAACAGCC AAGAACTGGGAACTCACAGCATCCGCCTCCACCAGC CGCCAGGTGTGTATCCACAGGGCCACAGCGACACCAC TGTAGCAGTGGCCGGCTGTGTTTTCTGCTGATCAGCG TCCTCCTCCTGAGTGGGCTCTCAAGGCAAATCCCCC GCTGGCCAGCGTTGAAATGGAAGCCATGGAGGCTCTG CCGGTGACTTGGGGGACCAGCAGCAGAGATGAAGAC TTGGAAAAGTCTCTCACCACCTA
347	IgESP-IL-15-L4- IL-15R α TM25	MDWTWILFLVAAATRVHSNWVNVISDLKKIEDLIQSMH IDATLYTESDVHPSCKVTAMKCFLELQVISLESGDASIH DTVENLILANNSLSSNGNVTESGCKECELEEKNIFEFL

	Amino Acid Sequence	QSFVHIVQMFINTSSGGGSGGGGSGGGGSGGGTLQITCP PPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLT ECVLNKATNVAHWTTPSLKCIRDPALVHQRPAAPPSTVTT AGVTPQPESLSPSGKEPAASSPSSNNTAATTAAIVPGSQL MPSKSPSTGTTEISSHESSHGTPSQTTAKNWELTASASHQ PPGVYPQGHSDTTVA VAGCVFLLISVLLLSGLSRQTPPLA SVEMEAMEALPVTWGTSSRDELENC SHHL
348	IgESP-IL-15-L4- IL-15R α TM25 Nucleic Acid Sequence	ATGGACTGGACCTGGATCCTCTTCTTGGTGGCAGCAG CCACGCGAGTCCACTCCAACCTGGGTGAACGTGATCTC CGACCTGAAGAAGATTGAAGATCTGATCCAGTCCATG CACATTGACGCCACCCTTTACACCGAGTCAGATGTGC ATCCGAGCTGCAAGGTCACCGCGATGAAGTGTTTCCT GCTGGAACCTCAAGTCATCAGCCTCGAATCCGGCGAC GCTTCAATTACAGACACTGTGGAGAACTTGATCATTCT GGCCAACAACCTCGCTGTCGTCCAATGGAAACGTGACC GAGTCCGGGTGCAAAGAGTGCGAAGAACTCGAGGAA AAGAACATCAAGGAGTTCCTGCAGTCCTTCGTGCACA TCGTGCAGATGTTTATCAACACTAGCTCTGGTGGTGGT TCTGGTGGGGGTGGCTCTGGCGGCGGGGGATCTGGTG GGGGTACTCTACAGATCACGTGCCCTCCCCCATGTC CGTGGAACACGCAGACATCTGGGTCAAGAGCTACAGC TTGTACTCCAGGGAGCGGTACATTTGTAACCTCTGGTTT CAAGCGTAAAGCCGGCACGTCCAGCCTGACGGAGTGC GTGTTGAACAAGGCCACGAATGTCGCCCACTGGACAA CCCCCAGTCTCAAATGCATTAGAGACCCTGCCCTGGT TCACCAAAGGCCAGCGCCACCCTCCACAGTAACGACG GCAGGGGTGACCCACAGCCAGAGAGCCTCTCCCCTT CTGGAAAAGAGCCCGCAGCTTCATCTCCCAGCTCAAA CAACACAGCGGCCACAACAGCAGCTATTGTCCCGGGC TCCCAGCTGATGCCTTCAAAATCACCTTCCACAGGAA CCACAGAGATAAGCAGTCATGAGTCCTCCACGGCAC CCCCTCTCAGACAACAGCCAAGAACTGGGAACTCACA GCATCCGCCTCCCACCAGCCGCCAGGTGTGTATCCAC AGGGCCACAGCGACACCACTGTAGCAGTGGCCGGCTG

		TGTTTTCTGCTGATCAGCGTCCTCCTCCTGAGTGGGC TCTCAAGGCCAAACTCCCCCGCTGGCCAGCGTTGAAAT GGAAGCCATGGAGGCTCTGCCGGTGACTTGGGGGACC AGCAGCAGAGATGAAGACTTGGAAGAACTGCTCTCACC ACCTA
349	IgESP-IL-15-L3- IL-15R α TM28 Amino Acid Sequence	MDWTWILFLVAAATRVHSNWVNVISDLKKIEDLIQSMH IDATLYTESDVHPSCKVTAMKCFLELQVISLESGDASIH DTVENLIILANNSLSSNGNVTESGCKECELEEKNIKEFL QSFVHIVQMFINTSSGGGSGGGGSGGGGSGGGGSGGGG SGGGTLQITCPPMMSVEHADIWVKSYSLYSRERYICNSGF KRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDPALVH QRPAPPSTVTTAGVTPQPESLSPSGKEPAASSPSSNNTAA TTAAIVPGSQLMPSKSPSTGTTEISSHESHGTPSQTTAKN WELTASASHQPPGVYPQGHSDTTFWVLVVVGGVLACY SLLVTVAFIIFWVKSRQTPPLASVEMEAMEALPVTWGTS SRDEDLNCSHHL
350	IgESP-IL-15-L3- IL-15R α TM28 Nucleic Acid Sequence	ATGGACTGGACCTGGATCCTCTTCTTGGTGGCAGCAG CCACGCGAGTCCACTCCAAGTGGGTGAACGTGATCTC CGACCTGAAGAAGATTGAAGATCTGATCCAGTCCATG CACATTGACGCCACCCTTTACACCGAGTCAGATGTGC ATCCGAGCTGCAAGGTCACCGCGATGAAGTGTTTCCT GCTGGAAGTCCAAGTCATCAGCCTCGAATCCGGCGAC GCTTCAATTACGACACTGTGGAGAACTTGATCATTCT GGCCAACAAGTCCGCTGTCGTCGAATGGAAACGTGACC GAGTCCGGGTGCAAAGAGTGCGAAGAACTCGAGGAA AAGAACATCAAGGAGTTCCTGCAGTCCTTCGTGCACA TCGTGCAGATGTTTATCAACACTAGCTCTGGTGGTGGT TCTGGTGGGGGTGGCTCTGGCGGCGGGGGATCAGGCG GAGGAGGGTCCGGAGGCGGAGGCTCTGGTGGGGGTA CTCTACAGATCACGTGCCCTCCCCCATGTCCGTGGA ACACGCAGACATCTGGGTCAAGAGCTACAGCTTGTA TCCAGGGAGCGGTACATTTGTAAGTCTGGTTTCAAGC GTAAAGCCGGCACGTCCAGCCTGACGGAGTGCGTGTT GAACAAGGCCACGAATGTCGCCCACTGGACAACCCCC

		AGTCTCAAATGCATTAGAGACCCTGCCCTGGTTCACC AAAGGCCAGCGCCACCCTCCACAGTAACGACGGCAG GGGTGACCCACAGCCAGAGAGCCTCTCCCCTTCTGG AAAAGAGCCCCGAGCTTCATCTCCAGCTCAAACAAC ACAGCGGCCACAACAGCAGCTATTGTCCCGGGCTCCC AGCTGATGCCTTCAAATCACCTTCCACAGGAACCAC AGAGATAAGCAGTCATGAGTCCTCCACGGCACCCCC TCTCAGACAACAGCCAAGAACTGGGAACACAGCAT CCGCCTCCCACCAGCCGCCAGGTGTGTATCCACAGGG CCACAGCGACACCACTTTTTGGGTGCTGGTGGTGGTT GGTGGAGTCCTGGCTTGCTATAGCTTGCTAGTAACAG TGGCCTTTATTATTTCTGGGTGAAGTCAAGGCAAAC CCCCGCTGGCCAGCGTTGAAATGGAAGCCATGGAGG CTCTGCCGGTGACTTGGGGGACCAGCAGCAGAGATGA AGACTTGGAAAACCTGCTCTCACACCTA
351	IgESP-IL-15-L1- IL-15R α dEx3 Amino Acid Sequence	MDWTWILFLVAAATRVHSNWVNVISDLKKIEDLIQSMH IDATLYTESDVHPSCKVTAMKCFLELQVISLESGDASIH DTVENLILANNSLSSNGNVTESGCKECEEELEKNIKEFL QSFVHIVQMFINTSKESGSVSSEQLAQFRSLDITCPPPMS VEHADIWVKSYSLSRERYICNSGFKRKAGTSSLTECVL NKATNVAHWTTPSLKCIKPAASSPSSNNTAATTAIVPG SQLMPSKSPSTGTTEISSHESSHGTPSQTAKNWELTASA SHQPPGVYPQGHSDTTVAISTSTVLLCGLSAVSLACYL KSRQTPPLASVEMEAMEALPVTWGTSSRDEDLNCSHH L
352	IgESP-IL-15-L1- IL-15R α dEx3 Nucleic Acid Sequence	ATGGACTGGACCTGGATCCTCTTCTTGGTGGCAGCAG CCACGCGAGTCCACTCCAACCTGGGTGAACGTGATCTC CGACCTGAAGAAGATTGAAGATCTGATCCAGTCCATG CACATTGACGCCACCCTTTACACCGAGTCAGATGTGC ATCCGAGCTGCAAGGTCACCGCGATGAAGTGTTTCCT GCTGGAACCTCCAAGTCATCAGCCTCGAATCCGGCGAC GCTTCAATTACGACACTGTGGAGAACTTGATCATTCT GGCCAACAACCTCGCTGTCGTCCAATGGAAACGTGACC GAGTCCGGGTGCAAAGAGTGCGAAGAACTCGAGGAA

		AAGAACATCAAGGAGTTCCTGCAGTCCTTCGTGCACA TCGTGCAGATGTTTATCAACACTAGCAAAGAGTCCGG CTCCGTGTCCTCCGAACAGCTGGCGCAGTTTCGTTCCT TGGATATCACGTGCCCTCCCCCATGTCCGTGGAACA CGCAGACATCTGGGTCAAGAGCTACAGCTTGTACTCC AGGGAGCGGTACATTTGTAACCTCTGGTTTCAAGCGTA AAGCCGGCACGTCCAGCCTGACGGAGTGCGTGTTGAA CAAGGCCACGAATGTCGCCCCTGGACAACCCCCAGT CTCAAATGCATTAAGCCCGCAGCTTCATCTCCCAGCTC AAACAACACAGCGGCCACAACAGCAGCTATTGTCCCG GGCTCCCAGCTGATGCCTTCAAATCACCTTCCACAG GAACCACAGAGATAAGCAGTCATGAGTCCTCCCACGG CACCCCCTCTCAGACAACAGCCAAGAAGTGGGAAGTC ACAGCATCCGCCTCCCACCAGCCGCCAGGTGTGTATC CACAGGGCCACAGCGACACCACTGTGGCTATCTCCAC GTCCACTGTCCTGCTGTGTGGGCTGAGCGCTGTGTCTC TCCTGGCATGCTACCTCAAGTCAAGGCAAAGTCCCCC GCTGGCCAGCGTTGAAATGGAAGCCATGGAGGCTCTG CCGGTGACTTGGGGGACCAGCAGCAGAGATGAAGAC TTGGAAAAGTCTCTCACCACCTA
353	IgESP-IL-15-L2- IL-15R α dEx3 Amino Acid Sequence	MDWTWILFLVAAATRVHSNWNVISDLKKIEDLIQSMH IDATLYTESDVHPSCKV TAMKCFLELQVISLESGDASIH DTVENLILANNSLSSNGNVTESGCKECELEEKNIKEFL QSFVHIVQMFINTEGKSSGSGSESKSTITCPPPM SVEHA DIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKAT NVAHWTTPSLKCIPKAASSPSSNNTAATTAIVPGS QLM PSKSPSTGTTEISSHESHGTPSQTTAKNWELTASASHQP PGVYPQGHSDTTVAISTSTVLLCGLSAVSLLACYLKS RQ TPPLASVEMEAMEALPVTWGTSSRDEDLENC SHHL
354	IgESP-IL-15-L2- IL-15R α dEx3 Nucleic Acid Sequence	ATGGACTGGACCTGGATCCTCTTCTTGGTGGCAGCAG CCACGCGAGTCCACTCCAAGTGGGTGAACGTGATCTC CGACCTGAAGAAGATTGAAGATCTGATCCAGTCCATG CACATTGACGCCACCCTTTACACCGAGTCAGATGTGC ATCCGAGCTGCAAGGTCACCGCGATGAAGTGTTTCCT

		GCTGGAAGTCCAAGTCATCAGCCTCGAATCCGGCGAC GCTTCAATTCACGACACTGTGGAGAACTTGATCATTCT GGCCAACAACCTCGCTGTCGTCCAATGGAAACGTGACC GAGTCCGGGTGCAAAGAGTGCGAAGAACTCGAGGAA AAGAACATCAAGGAGTTCCTGCAGTCCTTCGTGCACA TCGTGCAGATGTTTATCAACACTAGCGAAGGCAAATC CTCCGGCTCCGGCTCCGAATCCAAATCCACCATCACG TGCCCTCCCCCATGTCCGTGGAACACGCAGACATCT GGGTCAAGAGCTACAGCTTGTACTCCAGGGAGCGGTA CATTTGTAAGTCTGGTTTCAAGCGTAAAGCCGGCACG TCCAGCCTGACGGAGTGCGTGTTGAACAAGGCCACGA ATGTCGCCCAGTGGACAACCCCCAGTCTCAAATGCAT TAAGCCCGCAGCTTCATCTCCCAGCTCAAACAACACA GCGGCCACAACAGCAGCTATTGTCCCGGGCTCCCAGC TGATGCCTTCAAAATCACCTTCCACAGGAACCACAGA GATAAGCAGTCATGAGTCCTCCCACGGCACCCCTCT CAGACAACAGCCAAGAACTGGGAACTCACAGCATCC GCCTCCCACAGCCGCCAGGTGTGTATCCACAGGGCC ACAGCGACACCACTGTGGCTATCTCCACGTCCACTGT CCTGCTGTGTGGGCTGAGCGCTGTGTCTCTCCTGGCAT GCTACCTCAAGTCAAGGCAAACCTCCCCGCTGGCCAG CGTTGAAATGGAAGCCATGGAGGCTCTGCCGGTGACT TGGGGGACCAGCAGCAGAGATGAAGACTTGGAAGAAC TGCTCTCACCACCTA
355	IgESP-IL-15-L5-IL-15R α Amino Acid Sequence	MDWTWILFLVAAATRVHSNWVNVISDLKKIEDLIQSMH IDATLYTESDVHPSCKVTAMKCFLELQVISLESGDASIH DTVENLILANNSLSSNGNVTESGCKECELEEKNIKEFL QSFVHIVQMFINTSSGGGSGGGGSGGGGSGGGGSGGGG LQITCPPPMSVEHADIWVKSYSLSRERYICNSGFKRKA GTSSLTECVLNKATNVAHWTTPSLKCIRDPAHVHQRPA PSTVTTAGVTPQPELSPSGKEPAASSPSSNNTAATTAI VPGSQLMPKSPSTGTTEISSHESHGTPSQTAKNWELT ASASHQPPGVYPQGHSDTTVAISTSTVLLCGLSAVSLLA

		CYLKSRQTPPLASVEMEAMEALPVTWGTSSRDEDLENC SHHL
356	IgESP-IL-15-L5- IL-15R α Nucleic Acid Sequence	ATGGACTGGACCTGGATCCTCTTCTTGGTGGCAGCAG CCACGCGAGTCCACTCCAACCTGGGTGAACGTGATCTC CGACCTGAAGAAGATTGAAGATCTGATCCAGTCCATG CACATTGACGCCACCCTTTACACCGAGTCAGATGTGC ATCCGAGCTGCAAGGTCACCGCGATGAAGTGTTTCCT GCTGGAACCTCCAAGTCATCAGCCTCGAATCCGGCGAC GCTTCAATTACGACACTGTGGAGAACTTGATCATTCT GGCCAACAACCTCGCTGTCGTCCAATGGAAACGTGACC GAGTCCGGGTGCAAAGAGTGCGAAGAACTCGAGGAA AAGAACATCAAGGAGTTCCTGCAGTCCTTCGTGCACA TCGTGCAGATGTTTATCAACACTAGCAGCGGCGGCGG CAGCGGCGGCGGCGGCGGCGGCGGCGGCGGCGGCGG CGGCGGCGGCGGCGGCGGCGGCGGCGGCGGCGGCGG GTGCCCTCCCCCATGTCCGTGGAACACGCAGACATC TGGGTCAAGAGCTACAGCTTGTACTCCAGGGAGCGGT ACATTTGTAACCTCTGGTTTCAAGCGTAAAGCCGGCAC GTCCAGCCTGACGGAGTGCGTGTTGAACAAGGCCACG AATGTCGCCCCACTGGACAACCCCCAGTCTCAAATGCA TTAGAGACCCTGCCCTGGTTCACCAAAGGCCAGCGCC ACCCTCCACAGTAACGACGGCAGGGGTGACCCACAG CCAGAGAGCCTCTCCCCTTCTGGAAAAGAGCCCGCAG CTTCATCTCCCAGCTCAAACAACACAGCGGCCACAAC AGCAGCTATTGTCCCGGGCTCCCAGCTGATGCCTTCA AAATCACCTTCCACAGGAACCACAGAGATAAGCAGTC ATGAGTCCTCCACGGCACCCCCTCTCAGACAACAGC CAAGAACTGGGAACCTCACAGCATCCGCCTCCCACCAG CCGCCAGGTGTGTATCCACAGGGCCACAGCGACACCA CTGTGGCTATCTCCACGTCCACTGTCCTGCTGTGTGGG CTGAGCGCTGTGTCTCTCCTGGCATGCTACCTCAAGTC AAGGCAAACCTCCCCGCTGGCCAGCGTTGAAATGGAA GCCATGGAGGCTCTGCCGGTGAAGTTGGGGGACCAGCA

		GCAGAGATGAAGACTTGGAAAACCTGCTCTCACCACCT A
357	IgESP-IL-15-L3- IL-15R α TM25- WPREmut2 Nucleic Acid Sequence	ATGGACTGGACCTGGATCCTCTTCTTGGTGGCAGCAG CCACGCGAGTCCACTCCAACCTGGGTGAACGTGATCTC CGACCTGAAGAAGATTGAAGATCTGATCCAGTCCATG CACATTGACGCCACCCTTTACACCGAGTCAGATGTGC ATCCGAGCTGCAAGGTCACCGCGATGAAGTGTTTCCT GCTGGAACCTCCAAGTCATCAGCCTCGAATCCGGCGAC GCTTCAATTCACGACACTGTGGAGAACTTGATCATTCT GGCCAACAACCTCGCTGTCGTCCAATGGAAACGTGACC GAGTCCGGGTGCAAAGAGTGCGAAGAACTCGAGGAA AAGAACATCAAGGAGTTCCTGCAGTCCTTCGTGCACA TCGTGCAGATGTTTATCAACACTAGCTCTGGTGGTGGT TCTGGTGGGGGTGGCTCTGGCGGCGGGGGATCAGGCG GAGGAGGGTCCGGAGGCGGAGGCTCTGGTGGGGGTA CTCTACAGATCACGTGCCCTCCCCCATGTCCGTGGA ACACGCAGACATCTGGGTCAAGAGCTACAGCTTGTAC TCCAGGGAGCGGTACATTTGTAACCTCTGGTTTCAAGC GTAAAGCCGGCACGTCCAGCCTGACGGAGTGCGTGTT GAACAAGGCCACGAATGTCGCCCACTGGACAACCCCC AGTCTCAAATGCATTAGAGACCCTGCCCTGGTTCACC AAAGGCCAGCGCCACCCTCCACAGTAACGACGGCAG GGGTGACCCACAGCCAGAGAGCCTCTCCCCTTCTGG AAAAGAGCCCGCAGCTTCATCTCCAGCTCAAACAAC ACAGCGGCCACAACAGCAGCTATTGTCCCGGGCTCCC AGCTGATGCCTTCAAAATCACCTTCCACAGGAACCAC AGAGATAAGCAGTCATGAGTCCTCCACGGCACCCCC TCTCAGACAACAGCCAAGAACTGGGAACTCACAGCAT CCGCCTCCCACCAGCCGCCAGGTGTGTATCCACAGGG CCACAGCGACACCACTGTAGCAGTGGCCGGCTGTGTT TTCCTGCTGATCAGCGTCCTCCTCCTGAGTGGGCTCTC AAGGCAAACCTCCCCGCTGGCCAGCGTTGAAATGGAA GCCATGGAGGCTCTGCCGGTGAAGTTGGGGGACCAGCA GCAGAGATGAAGACTTGGAAAACCTGCTCTCACCACCT

		ATGAACCGGTCCGGAGCATCTTACCGCCATTTATACC CATATTTGTTCTGTTTTTCTTGATTTGGGTATACATTTA AATGTTAATAAAACAAAATGGTGGGGCAATCATTTAC ATTTTTTGGGATATGTAATTACTAGTTCAGGTGTATTG CCACAAGACAAACTTGTTAAGAACTTTCCCGTTATTT ACGCTCTGTTCCCTGTTAATCAACCTCTGGATTACAAAA TTTGTGAAAGATTGACTGATATTCTTAACCTTTGTTGCT CCTTTTACGCTGTGTGGATTTGCTGCTTTATTGCCTCT GTATCTTGCTATTGCTTCCCGTACGGCTTTCGTTTTCTC CTCCTTGTATAAATCCTGGTTGCTGTCTCTTTTTGAGG AGTTGTGGCCCGTTGTCCGTCAACGTGGCGTGGTGTG CTCTGTGTTTGCTGACGCAACCCCCACTGGCTGGGGC ATTGCCACCACCTGTCAACTCCTTTCTGGGACTTTCGC TTTCCCCCTCCCGATCGCCACGGCAGAACTCATCGCC GCCTGCCTTGCCCGCTGCTGGACAGGGGCTAGGTTGC TGGGCACTGATAATTCCGTGGTGTGTC
358	IgESP-IL-15-L1- IL-15R α - WPREmut2 Nucleic Acid Sequence	ATGGACTGGACCTGGATCCTCTTCTTGGTGGCAGCAG CCACGCGAGTCCACTCCAACCTGGGTGAACGTGATCTC CGACCTGAAGAAGATTGAAGATCTGATCCAGTCCATG CACATTGACGCCACCCTTTACACCGAGTCAGATGTGC ATCCGAGCTGCAAGGTCACCGCGATGAAGTGTTTCCT GCTGGAACCTCCAAGTCATCAGCCTCGAATCCGGCGAC GCTTCAATTACGACACTGTGGAGAACTTGATCATTCT GGCCAACAACCTCGCTGTCGTCCAATGGAAACGTGACC GAGTCCGGGTGCAAAGAGTGCGAAGAACTCGAGGAA AAGAACATCAAGGAGTTCCTGCAGTCCTTCGTGCACA TCGTGCAGATGTTTATCAACACTAGCAAAGAGTCCGG CTCCGTGTCCTCCGAACAGCTGGCGCAGTTTCGTTCCC TGGATATCACGTGCCCTCCCCCATGTCCGTGGAACA CGCAGACATCTGGGTCAAGAGCTACAGCTTGACTCC AGGGAGCGGTACATTTGTAACCTCTGGTTTCAAGCGTA AAGCCGGCACGTCCAGCCTGACGGAGTGCGTGTTGAA CAAGGCCACGAATGTCGCCCACTGGACAACCCCCAGT CTCAAATGCATTAGAGACCCTGCCCTGGTTCACCAAA

		GGCCAGCGCCACCCTCCACAGTAACGACGGCAGGGGT GACCCACAGCCAGAGAGCCTCTCCCCTTCTGGAAAA GAGCCCGCAGCTTCATCTCCCAGCTCAAACAACACAG CGGCCACAACAGCAGCTATTGTCCCGGGCTCCCAGCT GATGCCTTCAAAATCACCTTCCACAGGAACACAGAG ATAAGCAGTCATGAGTCCTCCCACGGCACCCCCTCTC AGACAACAGCCAAGAAGTGGGAACACAGCATCCG CCTCCCACCAGCCGCCAGGTGTGTATCCACAGGGCCA CAGCGACACCACTGTGGCTATCTCCACGTCCACTGTC CTGCTGTGTGGGCTGAGCGCTGTGTCTCTCTGGCATG CTACCTCAAGTCAAGGCAAACCTCCCCGCTGGCCAGC GTTGAAATGGAAGCCATGGAGGCTCTGCCGGTGACTT GGGGGACCAGCAGCAGAGATGAAGACTTGAAAACT GCTCTCACCACCTATGAACCGGTCCGGAGCATCTTAC CGCCATTTATACCCATATTTGTTCTGTTTTTCTTGATTT GGGTATACATTTAAATGTTAATAAAACAAAATGGTGG GGCAATCATTACATTTTTTGGGATATGTAATTACTAG TTCAGGTGTATTGCCACAAGACAAACTTGTTAAGAAA CTTTCCCGTTATTTACGCTCTGTTCTGTAAATCAACCT CTGGATTACAAAATTTGTGAAAGATTGACTGATATTC TTAACTTTGTTGCTCCTTTTACGCTGTGTGGATTTGCT GCTTTATTGCCTCTGTATCTTGCTATTGCTTCCCGTAC GGCTTTCGTTTTCTCCTCCTTGATAAAATCCTGGTTGCT GTCTCTTTTTGAGGAGTTGTGGCCCGTTGTCCGTCAAC GTGGCGTGGTGTGCTCTGTGTTTGCTGACGCAACCCCC ACTGGCTGGGGCATTGCCACCACCTGTCAACTCCTTTC TGGGACTTTCGCTTTCCCCCTCCCGATCGCCACGGCAG AACTCATCGCCGCCTGCCTTGCCCGCTGCTGGACAGG GGCTAGGTTGCTGGGCACTGATAATTCCGTGGTGTTG TC
359	IgESP-IL-15-L1- IL-15R α TM25- WPREmut2	ATGGACTGGACCTGGATCCTCTTCTTGGTGGCAGCAG CCACGCGAGTCCACTCCAAGTGGGTGAACGTGATCTC CGACCTGAAGAAGATTGAAGATCTGATCCAGTCCATG CACATTGACGCCACCCTTTACACCGAGTCAGATGTGC

	Nucleic Acid Sequence	ATCCGAGCTGCAAGGTCACCGCGATGAAGTGTTTCCT GCTGGA ACTCCAAGTCATCAGCCTCGAATCCGGCGAC GCTTCAATTCACGACACTGTGGAGAACTTGATCATTCT GGCCAACA ACTCGCTGTCGTCCAATGGAAACGTGACC GAGTCCGGGTGCAAAGAGTGCGAAGAACTCGAGGAA AAGAACATCAAGGAGTTCCTGCAGTCCTTCGTGCACA TCGTGCAGATGTTTATCAACACTAGCAAAGAGTCCGG CTCCGTGTCCTCCGAACAGCTGGCGCAGTTTCGTTCCC TGGATATCACGTGCCCTCCCCCATGTCCGTGGAACA CGCAGACATCTGGGTCAAGAGCTACAGCTTGTACTCC AGGGAGCGGTACATTTGTA ACTCTGGTTTCAAGCGTA AAGCCGGCACGTCCAGCCTGACGGAGTGCGTGTTGAA CAAGGCCACGAATGTCGCCCACTGGACAACCCCCAGT CTCAAATGCATTAGAGACCCTGCCCTGGTTCACCAAA GGCCAGCGCCACCCTCCACAGTAACGACGGCAGGGGT GACCCACAGCCAGAGAGCCTCTCCCCTTCTGGAAAA GAGCCCGCAGCTTCATCTCCCAGCTCAAACAACACAG CGGCCACAACAGCAGCTATTGTCCCGGGCTCCAGCT GATGCCTTCAAAATCACCTTCCACAGGAACACAGAG ATAAGCAGTCATGAGTCCTCCACGGCACCCCCTCTC AGACAACAGCCAAGAACTGGGAACTCACAGCATCCG CCTCCCACCAGCCGCCAGGTGTGTATCCACAGGGCCA CAGCGACACCACTGTAGCAGTGGCCGGCTGTGTTTTC CTGCTGATCAGCGTCCTCCTCCTGAGTGGGCTCTAAG GCAA ACTCCCCGCTGGCCAGCGTTGAAATGGAAGCC ATGGAGGCTCTGCCGGTGACTTGGGGGACCAGCAGCA GAGATGAAGACTTGGA AAACTGCTCTCACCACCTATG AACCGGTCCGGAGCATCTTACCGCCATTTATACCCAT ATTTGTTCTGTTTTTCTTGATTG GGTATACATTTAAAT GTTAATAAAACAAAATGGTGGGGCAATCATTTACATT TTTTGGGATATGTAATTACTAGTTCAGGTGTATTGCCA CAAGACAACTTGTTAAGAACTTTCCCGTTATTTAC GCTCTGTTCTGTTAATCAACCTCTGGATTACAAAATT TGTGAAAGATTGACTGATATTCTTA ACTTTGTGTCTCC
--	--------------------------	--

		TTTTACGCTGTGTGGATTGCTGCTTTATTGCCTCTGT ATCTTGCTATTGCTTCCCGTACGGCTTTCGTTTTCTCCT CCTTGTATAAATCCTGGTTGCTGTCTCTTTTTTGAGGAG TTGTGGCCCCGTTGTCCGTCAACGTGGCGTGGTGTGCTC TGTGTTTGCTGACGCAACCCCCACTGGCTGGGGCATT GCCACCACCTGTCAACTCCTTTCTGGGACTTTCGCTTT CCCCCTCCCGATCGCCACGGCAGAACTCATCGCCGCC TGCCTTGCCCGCTGCTGGACAGGGGCTAGGTTGCTGG GCACTGATAATTCCGTGGTGTGTC
360	IgESP-IL-15-L2- IL-15R α - WPREmut2 Nucleic Acid Sequence	ATGGACTGGACCTGGATCCTCTTCTTGGTGGCAGCAG CCACGCGAGTCCACTCCAAGTGGGTGAACGTGATCTC CGACCTGAAGAAGATTGAAGATCTGATCCAGTCCATG CACATTGACGCCACCCTTTACACCGAGTCAGATGTGC ATCCGAGCTGCAAGGTCACCGCGATGAAGTGTTCCT GCTGGAAGTCCAAGTCATCAGCCTCGAATCCGGCGAC GCTTCAATTACGACACTGTGGAGAACTTGATCATTCT GGCCAACAAGTCTGCTGTCGTCGAATGGAAACGTGACC GAGTCCGGGTGCAAAGAGTGCGAAGAACTCGAGGAA AAGAACATCAAGGAGTTCCTGCAGTCCTTCGTGCACA TCGTGCAGATGTTTATCAACACTAGCGAAGGCCAAATC CTCCGGCTCCGGCTCCGAATCCAAATCCACCATCACG TGCCCTCCCCCATGTCCGTGGAACACGCAGACATCT GGGTCAAGAGCTACAGCTTGTACTCCAGGGAGCGGTA CATTTGTAAGTCTGGTTTCAAGCGTAAAGCCGGCACG TCCAGCCTGACGGAGTGCGTGTTGAACAAGGCCACGA ATGTCGCCCCACTGGACAACCCCCAGTCTCAAATGCAT TAGAGACCCTGCCCTGGTTCACCAAAGGCCAGCGCCA CCCTCCACAGTAACGACGGCAGGGGTGACCCACAGC CAGAGAGCCTCTCCCCTTCTGGAAAAGAGCCCGCAGC TTCATCTCCCAGCTCAAACAACACAGCGGCCACAACA GCAGCTATTGTCCCGGGCTCCAGCTGATGCCTTCAA AATCACCTTCCACAGGAACACAGAGATAAGCAGTCA TGAGTCCTCCACGGCACCCCCTCTCAGACAACAGCC AAGAACTGGGAACTCACAGCATCCGCCTCCCACCAGC

		CGCCAGGTGTGTATCCACAGGGCCACAGCGACACCAC TGTGGCTATCTCCACGTCCACTGTCCTGCTGTGTGGGC TGAGCGCTGTGTCTCTCCTGGCATGCTACCTCAAGTCA AGGCAAACCTCCCCGCTGGCCAGCGTTGAAATGGAAG CCATGGAGGCTCTGCCGGTGACTTGGGGGACCAGCAG CAGAGATGAAGACTTGGAAAACCTGCTCTCACCACCTA TGAACCGGTCCGGAGCATCTTACCGCCATTTATACCC ATATTTGTTCTGTTTTTCTTGATTTGGGTATACATTTAA ATGTTAATAAAACAAAATGGTGGGGCAATCATTTACA TTTTTTGGGATATGTAATTACTAGTTCAGGTGTATTGC CACAAGACAACTTGTTAAGAACTTTCCCGTTATTT ACGCTCTGTTCTGTTAATCAACCTCTGGATTACAAAA TTTGTGAAAGATTGACTGATATTCTTAACCTTTGTTGCT CCTTTTACGCTGTGTGGATTTGCTGCTTTATTGCCTCT GTATCTTGCTATTGCTTCCCGTACGGCTTTCGTTTTCTC CTCCTTGTATAAATCCTGGTTGCTGTCTCTTTTTGAGG AGTTGTGGCCCGTTGTCCGTCAACGTGGCGTGGTGTG CTCTGTGTTTGCTGACGCAACCCCCACTGGCTGGGGC ATTGCCACCACCTGTCAACTCCTTTCTGGGACTTTCGC TTCCCCCTCCCGATCGCCACGGCAGAACTCATCGCC GCCTGCCTTGCCCGCTGCTGGACAGGGGCTAGGTTGC TGGGCACTGATAATTCCGTGGTGTGTC
361	IgESP-IL-15-L2- IL-15R α TM25- WPREmut2 Nucleic Acid Sequence	ATGGACTGGACCTGGATCCTCTTCTTGGTGGCAGCAG CCACGCGAGTCCACTCCAACCTGGGTGAACGTGATCTC CGACCTGAAGAAGATTGAAGATCTGATCCAGTCCATG CACATTGACGCCACCCTTTACACCGAGTCAGATGTGC ATCCGAGCTGCAAGGTCACCGCGATGAAGTGTTTCCT GCTGGAACCTCCAAGTCATCAGCCTCGAATCCGGCGAC GCTTCAATTACGACACTGTGGAGAACTTGATCATTCT GGCCAACAACCTCGCTGTCGTCCAATGGAAACGTGACC GAGTCCGGGTGCAAAGAGTGCGAAGAACTCGAGGAA AAGAACATCAAGGAGTTCCTGCAGTCCTTCGTGCACA TCGTGCAGATGTTTATCAACACTAGCGAAGGCAAATC CTCCGGCTCCGGCTCCGAATCCAAATCCACCATCACG

		TGCCCTCCCCCATGTCCGTGGAACACGCAGACATCT GGGTCAAGAGCTACAGCTTGTACTCCAGGGAGCGGTA CATTTGTAACCTCTGGTTTCAAGCGTAAAGCCGGCACG TCCAGCCTGACGGAGTGCGTGTTGAACAAGGCCACGA ATGTCGCCCCACTGGACAACCCCCAGTCTCAAATGCAT TAGAGACCCTGCCCTGGTTCACCAAAGGCCAGCGCCA CCCTCCACAGTAACGACGGCAGGGGTGACCCACAGC CAGAGAGCCTCTCCCCTTCTGAAAAAGAGCCCGCAGC TTCATCTCCCAGCTCAAACAACACAGCGGCCACAACA GCAGCTATTGTCCCGGGCTCCCAGCTGATGCCTTCAA AATCACCTTCCACAGGAACCACAGAGATAAGCAGTCA TGAGTCCTCCCACGGCACCCCCTCTCAGACAACAGCC AAGAACTGGGAACTCACAGCATCCGCCTCCCACCAGC CGCCAGGTGTGTATCCACAGGGCCACAGCGACACCAC TGTAGCAGTGGCCGGCTGTGTTTTCTGCTGATCAGCG TCCTCCTCCTGAGTGGGCTCTCAAGGCAAACCTCCCC GCTGGCCAGCGTTGAAATGGAAGCCATGGAGGCTCTG CCGGTGACTTGGGGGACCAGCAGCAGAGATGAAGAC TTGGAAAACCTGCTCTCACCACCTATGAACCGGTCCGG AGCATCTTACCGCCATTTATACCCATATTTGTTCTGTT TTTCTTGATTTGGGTATACATTTAAATGTTAATAAAAC AAAATGGTGGGGCAATCATTTACATTTTTTTGGGATAT GTAATTACTAGTTCAGGTGTATTGCCACAAGACAAAC TTGTTAAGAACTTTCCCGTTATTTACGCTCTGTTCT GTTAATCAACCTCTGGATTACAAAATTTGTGAAAGAT TGA CTGATATTCTTAACTTTGTTGCTCCTTTTACGCTGT GTGGATTTGCTGCTTTATTGCCTCTGTATCTTGCTATT GCTTCCCGTACGGCTTTCGTTTTCTCCTCCTTGATAA ATCCTGGTTGCTGTCTCTTTTTGAGGAGTTGTGGCCCG TTGTCCGTCAACGTGGCGTGGTGTGCTCTGTGTTTGCT GACGCAACCCCCACTGGCTGGGGCATTGCCACCACCT GTCAACTCCTTTCTGGGACTTTCGCTTTCCCCCTCCCG ATCGCCACGGCAGAACTCATCGCCGCCTGCCTTGCCC
--	--	---

		GCTGCTGGACAGGGGCTAGGTTGCTGGGCACTGATAA TTCCGTGGTGTGTC
362	IgESP-IL-15-L4- IL-15R α TM25- WPREmut2 Nucleic Acid Sequence	ATGGACTGGACCTGGATCCTCTTCTTGGTGGCAGCAG CCACGCGAGTCCACTCCAACCTGGGTGAACGTGATCTC CGACCTGAAGAAGATTGAAGATCTGATCCAGTCCATG CACATTGACGCCACCCTTTACACCGAGTCAGATGTGC ATCCGAGCTGCAAGGTCACCGCGATGAAGTGTTCCT GCTGGAACCTCCAAGTCATCAGCCTCGAATCCGGCGAC GCTTCAATTCACGACACTGTGGAGAACTTGATCATTCT GGCCAACAACCTCGCTGTCGTCCAATGGAAACGTGACC GAGTCCGGGTGCAAAGAGTGCGAAGAACTCGAGGAA AAGAACATCAAGGAGTTCCTGCAGTCCTTCGTGCACA TCGTGCAGATGTTTATCAACACTAGCTCTGGTGGTGGT TCTGGTGGGGGTGGCTCTGGCGGCGGGGGATCTGGTG GGGGTACTCTACAGATCACGTGCCCTCCCCCATGTC CGTGGAACACGCAGACATCTGGGTCAAGAGCTACAGC TTGTACTCCAGGGAGCGGTACATTTGTAACCTCTGGTTT CAAGCGTAAAGCCGGCACGTCCAGCCTGACGGAGTGC GTGTTGAACAAGGCCACGAATGTCGCCCCACTGGACAA CCCCCAGTCTCAAATGCATTAGAGACCCTGCCCTGGT TCACCAAAGGCCAGCGCCACCCTCCACAGTAACGACG GCAGGGGTGACCCACAGCCAGAGAGCCTCTCCCCTT CTGGAAAAGAGCCCGCAGCTTCATCTCCCAGCTCAAA CAACACAGCGGCCACAACAGCAGCTATTGTCCCGGGC TCCCAGCTGATGCCTTCAAAATCACCTTCCACAGGAA CCACAGAGATAAGCAGTCATGAGTCCTCCACGGCAC CCCCTCTCAGACAACAGCCAAGAACTGGGAACTCACA GCATCCGCCTCCCACCAGCCGCCAGGTGTGTATCCAC AGGGCCACAGCGACACCACTGTAGCAGTGGCCGGCTG TGTTTTCTGCTGATCAGCGTCCTCCTCCTGAGTGGGC TCTCAAGGCAAACCTCCCCGCTGGCCAGCGTTGAAAT GGAAGCCATGGAGGCTCTGCCGGTGACTTGGGGGACC AGCAGCAGAGATGAAGACTTGGAACCTGCTCTCACC ACCTATGAACCGGTCCGGAGCATCTTACCGCCATTTA

		TACCCATATTTGTTCTGTTTTTCTTGATTGGGTATACA TTTAAATGTTAATAAAACAAAATGGTGGGGCAATCAT TTACATTTTTTGGGATATGTAATTACTAGTTCAGGTGT ATTGCCACAAGACAAACTTGTTAAGAACTTTCCCGT TATTTACGCTCTGTTCTGTAAATCAACCTCTGGATTA CAAAATTTGTGAAAGATTGACTGATATTCTTAACCTTTG TTGCTCCTTTTACGCTGTGTGGATTGCTGCTTTATTGC CTCTGTATCTTGCTATTGCTTCCCGTACGGCTTTCGTTT TCTCCTCCTTGATAAATCCTGGTTGCTGTCTCTTTTTG AGGAGTTGTGGCCCGTTGTCCGTCAACGTGGCGTGGT GTGCTCTGTGTTTGCTGACGCAACCCCCACTGGCTGG GGCATTGCCACCACCTGTCAACTCCTTTCTGGGACTTT CGCTTTCCCCCTCCCGATCGCCACGGCAGAACTCATC GCCGCCTGCCTTGCCCGCTGCTGGACAGGGGCTAGGT TGCTGGGCACTGATAATTCCGTGGTGTGTC
363	IgESP-IL-15-L3- IL-15RαTM28- WPREmut2 Nucleic Acid Sequence	ATGGACTGGACCTGGATCCTCTTCTTGGTGGCAGCAG CCACGCGAGTCCACTCCAACCTGGGTGAACGTGATCTC CGACCTGAAGAAGATTGAAGATCTGATCCAGTCCATG CACATTGACGCCACCCTTTACACCGAGTCAGATGTGC ATCCGAGCTGCAAGGTCACCGCGATGAAGTGTTCCT GCTGGAACCTCAAGTCATCAGCCTCGAATCCGGCGAC GCTTCAATTACGACACTGTGGAGAACTTGATCATTCT GGCCAACAACCTCGCTGTCGTCCAATGGAAACGTGACC GAGTCCGGGTGCAAAGAGTGCGAAGAACTCGAGGAA AAGAACATCAAGGAGTTCCTGCAGTCCTTCGTGCACA TCGTGCAGATGTTTATCAACACTAGCTCTGGTGGTGGT TCTGGTGGGGGTGGCTCTGGCGGCGGGGGATCAGGCG GAGGAGGGTCCGGAGGCGGAGGCTCTGGTGGGGGT CTCTACAGATCACGTGCCCTCCCCCATGTCCGTGGA ACACGCAGACATCTGGGTCAAGAGCTACAGCTTGAC TCCAGGGAGCGGTACATTTGTAACCTCTGGTTTCAAGC GTAAAGCCGGCACGTCCAGCCTGACGGAGTGCGTGTT GAACAAGGCCACGAATGTCGCCCACTGGACAACCCCC AGTCTCAAATGCATTAGAGACCCTGCCCTGGTTCACC

		AAAGGCCAGCGCCACCCTCCACAGTAACGACGGCAG GGGTGACCCACAGCCAGAGAGCCTCTCCCCTTCTGG AAAAGAGCCCGCAGCTTCATCTCCAGCTCAAACAAC ACAGCGGCCACAACAGCAGCTATTGTCCCGGGCTCCC AGCTGATGCCTTCAAAATCACCTTCCACAGGAACCAC AGAGATAAGCAGTCATGAGTCCTCCACGGCACCCCC TCTCAGACAACAGCCAAGAACTGGGAACTCACAGCAT CCGCCTCCCACCAGCCGCCAGGTGTGTATCCACAGGG CCACAGCGACACCACTTTTTGGGTGCTGGTGGTGGTT GGTGGAGTCCTGGCTTGCTATAGCTTGCTAGTAACAG TGGCCTTTATTATTTCTGGGTGAAGTCAAGGCAAAC CCCCGCTGGCCAGCGTTGAAATGGAAGCCATGGAGG CTCTGCCGGTGACTTGGGGGACCAGCAGCAGAGATGA AGACTTGGAAGAACTGCTCTCACCACTATGAACCGGT CCGGAGCATCTTACCGCCATTTATACCCATATTTGTTC TGTTTTCTTGATTTGGGTATACATTTAAATGTTAATA AAACAAAATGGTGGGGCAATCATTTACATTTTTTGGG ATATGTAATTACTAGTTCAGGTGTATTGCCACAAGAC AACTTGTTAAGAACTTTCCCGTTATTTACGCTCTGT TCCTGTTAATCAACCTCTGGATTACAAAATTTGTGAAA GATTGACTGATATTCTTAACCTTTGTTGCTCCTTTTACG CTGTGTGGATTTGCTGCTTTATTGCCTCTGTATCTTGCT ATTGCTTCCCGTACGGCTTTCGTTTTCTCCTCCTTGAT AAATCCTGGTTGCTGTCTCTTTTTGAGGAGTTGTGGCC CGTTGTCCGTCAACGTGGCGTGGTGTGCTCTGTGTTTG CTGACGCAACCCCCACTGGCTGGGGCATTGCCACCAC CTGTCAACTCCTTTCTGGGACTTTCGCTTTCCCCCTCC CGATCGCCACGGCAGAACTCATCGCCGCCTGCCTTGC CCGCTGCTGGACAGGGGCTAGGTTGCTGGGCACTGAT AATTCCGTGGTGTGTC
364	IgESP-IL-15-L1- IL-15RadEx3- WPREmut2	ATGGACTGGACCTGGATCCTCTTCTTGGTGGCAGCAG CCACGCGAGTCCACTCCAAGTGGGTGAACGTGATCTC CGACCTGAAGAAGATTGAAGATCTGATCCAGTCCATG CACATTGACGCCACCCTTTACACCGAGTCAGATGTGC

	Nucleic Acid Sequence	ATCCGAGCTGCAAGGTCACCGCGATGAAGTGTTTCCT GCTGGAAC TCCAAGTCATCAGCCTCGAATCCGGCGAC GCTTCAATTACGACACTGTGGAGAACTTGATCATTCT GGCCAACAAC TCGCTGTCGTCCAATGGAAACGTGACC GAGTCCGGGTGCAAAGAGTGCGAAGAACTCGAGGAA AAGAACATCAAGGAGTTCCTGCAGTCCTTCGTGCACA TCGTGCAGATGTTTATCAACACTAGCAAAGAGTCCGG CTCCGTGTCCTCCGAACAGCTGGCGCAGTTTCGTTCCC TGGATATCACGTGCCCTCCCCCATGTCCGTGGAACA CGCAGACATCTGGGTCAAGAGCTACAGCTTGACTCC AGGGAGCGGTACATTTGTA ACTCTGGTTTCAAGCGTA AAGCCGGCACGTCCAGCCTGACGGAGTGCGTGTTGAA CAAGGCCACGAATGTCGCCCACTGGACAACCCCCAGT CTCAAATGCATTAAGCCCGCAGCTTCATCTCCAGCTC AAACAACACAGCGGCCACAACAGCAGCTATTGTCCCG GGCTCCCAGCTGATGCCTTCAA AATCACCTTCCACAG GAACCACAGAGATAAGCAGTCATGAGTCCTCCACGG CACCCCCTCTCAGACAACAGCCAAGAACTGGGAACTC ACAGCATCCGCCTCCCACCAGCCGCCAGGTGTGTATC CACAGGGCCACAGCGACACCACTGTGGCTATCTCCAC GTCCACTGTCTGTGTGTGGGCTGAGCGCTGTGTCTC TCCTGGCATGCTACCTCAAGTCAAGGCAA ACTCCCC GCTGGCCAGCGTTGAAATGGAAGCCATGGAGGCTCTG CCGGTGACTTGGGGGACCAGCAGCAGAGATGAAGAC TTGGAAA ACTGCTCTCACCACCTATGAACCGGTCCGG AGCATCTTACCGCCATTTATACCCATATTTGTTCTGTT TTTCTTGATTTGGGTATACATTTAAATGTTAATAAAAC AAAATGGTGGGGCAATCATTTACATTTTTTGGGATAT GTAATTACTAGTTCAGGTGTATTGCCACAAGACAAAC TTGTTAAGAACTTTCCCGTTATTTACGCTCTGTTCT GTTAATCAACCTCTGGATTACAAAATTTGTGAAAGAT TGA CTGATATTCTTA ACTTTGTTGCTCCTTTTACGCTGT GTGGATTTGCTGCTTTATTGCCTCTGTATCTTGCTATT GCTTCCCGTACGGCTTTCGTTTTCTCCTCCTTGATAA
--	--------------------------	--

		ATCCTGGTTGCTGTCTCTTTTTGAGGAGTTGTGGCCCG TTGTCCGTCAACGTGGCGTGGTGTGCTCTGTGTTTGCT GACGCAACCCCCACTGGCTGGGGCATTGCCACCACCT GTCAACTCCTTTCTGGGACTTTCGCTTTCCCCCTCCCG ATCGCCACGGCAGAACTCATCGCCGCCTGCCTTGCCC GCTGCTGGACAGGGGCTAGGTTGCTGGGCACTGATAA TTCCGTGGTGTGTGTC
365	IgESP-IL-15-L2- IL-15R α dEx3- WPREmut2 Nucleic Acid Sequence	ATGGACTGGACCTGGATCCTCTTCTTGGTGGCAGCAG CCACGCGAGTCCACTCCAAGTGGGTGAACGTGATCTC CGACCTGAAGAAGATTGAAGATCTGATCCAGTCCATG CACATTGACGCCACCCTTTACACCGAGTCAGATGTGC ATCCGAGCTGCAAGGTCACCGCGATGAAGTGTTCCT GCTGGAAGTCCAAGTCATCAGCCTCGAATCCGGCGAC GCTTCAATTACGACACTGTGGAGAACTTGATCATTCT GGCCAACAAGTCTGCTGTCGTTCAATGGAAACGTGACC GAGTCCGGGTGCAAAGAGTGCGAAGAACTCGAGGAA AAGAACATCAAGGAGTTCCTGCAGTCCTTCGTGCACA TCGTGCAGATGTTTATCAACACTAGCGAAGGCCAAATC CTCCGGCTCCGGCTCCGAATCCAAATCCACCATCACG TGCCCTCCCCCATGTCCGTGGAACACGCAGACATCT GGGTCAAGAGCTACAGCTTGTACTCCAGGGAGCGGTA CATTTGTAAGTCTGGTTTCAAGCGTAAAGCCGGCACG TCCAGCCTGACGGAGTGCGTGTTGAACAAGGCCACGA ATGTCGCCCCACTGGACAACCCCCAGTCTCAAATGCAT TAAGCCCGCAGCTTCATCTCCAGCTCAAACAACACA GCGGCCACAACAGCAGCTATTGTCCCGGGCTCCCAGC TGATGCCTTCAAATCACCTTCCACAGGAACACAGA GATAAGCAGTCATGAGTCCTCCACGGCACCCCTCT CAGACAACAGCCAAGAACTGGGAACTCACAGCATCC GCCTCCCACAGCCGCCAGGTGTGTATCCACAGGGCC ACAGCGACACCACTGTGGCTATCTCCACGTCCACTGT CCTGCTGTGTGGGCTGAGCGCTGTGTCTCTCCTGGCAT GCTACCTCAAGTCAAGGCAAAGTCCCCCGCTGGCCAG CGTTGAAATGGAAGCCATGGAGGCTCTGCCGGTGACT

		TGGGGGACCAGCAGCAGAGATGAAGACTTGGAAAAC TGCTCTCACCACCTATGAACCGGTCCGGAGCATCTTA CCGCCATTTATACCCATATTTGTTCTGTTTTTCTTGATT TGGGTATACATTTAAATGTTAATAAAACAAAATGGTG GGGCAATCATTACATTTTTTGGGATATGTAATTACTA G TTCAGGTGTATTGCCACAAGACAAACTTGTTAAGAA ACTTTCCCGTTATTTACGCTCTGTTCTGTTAATCAAC CTCTGGATTACAAAATTTGTGAAAGATTGACTGATAT TCTTAAC TTTGTTGCTCCTTTTACGCTGTGTGGATTTGC TGCTTTATTGCCTCTGTATCTTGCTATTGCTTCCCGTAC GGCTTTCGTTTTTCTCCTCCTTGTATAAATCCTGGTTGCT GTCTCTTTTTGAGGAGTTGTGGCCCGTTGTCCGTCAAC GTGGCGTGGTGTGCTCTGTGTTTGCTGACGCAACCCCC ACTGGCTGGGGCATTGCCACCACCTGTCAACTCCTTTC TGGGACTTTCGCTTTCCCCCTCCCGATCGCCACGGCAG AACTCATCGCCGCCTGCCTTGCCCGCTGCTGGACAGG GGCTAGGTTGCTGGGCACTGATAATTCCGTGGTGTTG TC
366	IgESP-IL-15-L5- IL-15Rα-WPRE Nucleic Acid Sequence	ATGGACTGGACCTGGATCCTCTTCTTGGTGGCAGCAG CCACGCGAGTCCACTCCAACCTGGGTGAACGTGATCTC CGACCTGAAGAAGATTGAAGATCTGATCCAGTCCATG CACATTGACGCCACCCTTTACACCGAGTCAGATGTGC ATCCGAGCTGCAAGGTCACCGCGATGAAGTGTTTCCT GCTGGAAC TCCAAGTCATCAGCCTCGAATCCGGCGAC GCTTCAATTACGACACTGTGGAGAACTTGATCATTCT GGCCAACAAC TCGCTGTCGTCCAATGGAAACGTGACC GAGTCCGGGTGCAAAGAGTGCGAAGAACTCGAGGAA AAGAACATCAAGGAGTTCCTGCAGTCCTTCGTGCACA TCGTGCAGATGTTTATCAACACTAGCAGCGGCGGCGG CAGCGGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGG CGGCGGCGGCAGCGGCGGCGGCAGCCTACAGATCAC GTGCCCTCCCCCATGTCCGTGGAACACGCAGACATC TGGGTCAAGAGCTACAGCTTGTACTCCAGGGAGCGGT ACATTTGTAAC TCTGGTTTCAAGCGTAAAGCCGGCAC

		GTCCAGCCTGACGGAGTGCGTGTTGAACAAGGCCACG AATGTCGCCCAGTGGACAACCCCCAGTCTCAAATGCA TTAGAGACCCTGCCCTGGTTCACCAAAGGCCAGCGCC ACCCTCCACAGTAACGACGGCAGGGGTGACCCACAG CCAGAGAGCCTCTCCCCTTCTGGAAAAGAGCCCGCAG CTTCATCTCCCAGCTCAAACAACACAGCGGCCACAAC AGCAGCTATTGTCCCGGGCTCCCAGCTGATGCCTTCA AAATCACCTTCCACAGGAACCACAGAGATAAGCAGTC ATGAGTCCTCCCACGGCACCCCCTCTCAGACAACAGC CAAGAACTGGGAACTCACAGCATCCGCCTCCCACCAG CCGCCAGGTGTGTATCCACAGGGCCACAGCGACACCA CTGTGGCTATCTCCACGTCCACTGTCCTGCTGTGTGGG CTGAGCGCTGTGTCTCTCCTGGCATGCTACCTCAAGTC AAGGCAAACCTCCCCGCTGGCCAGCGTTGAAATGGAA GCCATGGAGGCTCTGCCGGTGACTTGGGGGACCAGCA GCAGAGATGAAGACTTGGA AAACTGCTCTCACCACCT ATGATGAACCGGTCCGCAGTCTGACGTACGCGTAATC AACCTCTGGATTACAAAATTTGTGAAAGATTGACTGG TATTCTTA ACTATGTTGCTCCTTTTACGCTATGTGGAT ACGCTGCTTTAATGCCTTTGTATCATGCTATTGCTTCC CGTATGGCTTTCA TTTTCTCCTCCTTGTATAAATCCTG GTTGCTGTCTCTTTATGAGGAGTTGTGGCCCGTTGTCA GGCAACGTGGCGTGGTGTGCACTGTGTTTGCTGACGC AACCCCCACTGGTTGGGGCATTGCCACCACCTGTCAG CTCCTTTCCGGGACTTTTCGCTTTCCCCCTCCCTATTGCC ACGGCGGAACTCATCGCCGCCTGCCTTGCCCGCTGCT GGACAGGGGCTCGGCTGTTGGGCACTGACAATTCCGT GGTGTGTGTCGGGGAAGCTGACGTCCTTTCCATGGCTG CTCGCCTGTGTTGCCACCTGGATTCTGCGCGGGACGTC CTTCTGCTACGTCCCTTCGGCCCTCAATCCAGCGGACC TTCCTTCCCGCGGCCTGCTGCCGGCTCTGCGGCCTCTT CCGCGTCTTCGCCTTCGCCCTCAGACGAGTCGGATCTC CCTTTGGGCGCCTCCCCGCC
--	--	--

367	IgE Signal Peptide Amino Acid Sequence	MDWTWILFLVAAATRVHS
368	IgE Signal Peptide Nucleic Acid Sequence	ATGGACTGGACCTGGATCCTCTTCTTGGTGGCAGCAG CCACGCGAGTCCACTCC
369	IL-15 Signal Peptide Amino Acid Sequence	MRISKPHLRSISIQCYLCLLNSHFLTEA
370	IL-15R α Signal Peptide Amino Acid Sequence	MAPRRARGCRTLGLPALLLLLLLRPPATRG
371	IL-15 Propeptide Amino Acid Sequence	GIHVFILGCFSAGLPKTEA
372	CD25 Transmembrane Domain Amino Acid Sequence	VAVAGCVFLLISVLLLSGL
373	CD25 Transmembrane Domain Nucleic Acid Sequence	GTAGCAGTGGCCGGCTGTGTTTTCTGCTGATCAGCGT CCTCCTCCTGAGTGGGCTC
374	CD28 Transmembrane Domain Amino Acid Sequence	FWVLVVVGGVLACYSLLVTVAFIIFWV
375	CD28 Transmembrane Domain Nucleic Acid Sequence	TTTGGGTGCTGGTGGTGGTTGGTGGAGTCCTGGCTTG CTATAGCTTGCTAGTAACAGTGGCCTTTATTATTTCT GGGTG
376	IL-15R α Transmembrane	VAISTSTVLLCGLSAVSLLACYL

	Domain Amino Acid Sequence 1	
377	IL-15R α Transmembrane Domain Nucleic Acid Sequence 1	GTGGCTATCTCCACGTCCACTGTCCTGCTGTGTGGGCT GAGCGCTGTGTCTCTCCTGGCATGCTACCTC
378	IL-15R α Transmembrane Domain Amino Acid Sequence 2	VAISTSTVLLCGLSAVSLLACYLK
379	IL-15R α Transmembrane Domain Nucleic Acid Sequence 2	GTGGCTATCTCCACGTCCACTGTCCTGCTGTGTGGGCT GAGCGCTGTGTCTCTCCTGGCATGCTACCTCAAG
380	Wild Type IL-15 Propeptide Nucleic Acid Sequence	GGCATTTCATGTCTTCATTTTGGGCTGTTTCAGTGCAGG GCTTCCTAAAACAGAAGCC
381	IL-15 Signal Peptide Nucleic Acid Sequence	ATGAGAATTTCGAAACCACATTTGAGAAGTATTTCCA TCCAGTGCTACTTGTGTTTACTTCTAAACAGTCATTTT CTAACTGAAGCT
382	Kozak Sequence	GCCNCCATGG where N is a purine (A or G)
383	Linker L1 Amino Acid Sequence	KESGSVSSEQLAQFRSLD
384	Linker L1 Nucleic Acid Sequence	AAAGAGTCCGGCTCCGTGTCCTCCGAACAGCTGGCGC AGTTTCGTTCCCTGGAT
385	Linker L2 Amino Acid Sequence	EGKSSGSGSESKST
386	Linker L2 Nucleic Acid Sequence	GAAGGCAAATCCTCCGGCTCCGGCTCCGAATCCAAAT CCACC
387	Linker L3 Amino Acid Sequence	SGGSGGGGSGGGGSGGGGSGGGGSGGGTLQ

388	Linker L3 Nucleic Acid Sequence	TCTGGTGGTGGTTCTGGTGGGGGTGGCTCTGGCGGCG GGGGATCAGGCGGAGGAGGGTCCGGAGGCGGAGGCT CTGGTGGGGGTACTCTACAG
389	Linker L4 Amino Acid Sequence	SGGSGGGGSGGGSGGGTLQ
390	Linker L4 Nucleic Acid Sequence	TCTGGTGGTGGTTCTGGTGGGGGTGGCTCTGGCGGCG GGGGATCTGGTGGGGGTACTCTACAG
391	Linker L5 Amino Acid Sequence	SGGSGGGGSGGGSGGGSGGGSLQ
392	Linker L5 Nucleic Acid Sequence	AGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCGGC GGCGGCAGCGGCGGCGGCGGCAGCGGCGGCGGCAGC CTACAG
393	Linker 6 Amino Acid Sequence	GGGSGGGGSGGGGS
394	Linker 6 Nucleic Acid Sequence	GGCGGCGGCGGCAGCGGCGGCGGCGGCAGCGGCGGC GGCGGCAGC
395	Linker Amino Acid Sequence	SGSGGGGSGGGSGGGSLQ
396	Linker Amino Acid Sequence	GSGSGSGS
397	Linker Amino Acid Sequence	GGSGSGSGG
398	Linker Amino Acid Sequence	GGSGG
399	Linker Amino Acid Sequence	GGGGGGGG
400	Linker Amino Acid Sequence	GGGGGG
401	Linker Amino Acid Sequence	GGGGS
402	Linker Amino Acid Sequence	GGGSGGGGS

403	Linker Amino Acid Sequence	GGSGGHMGSGG
404	Linker Amino Acid Sequence	EAAAKEEAAKEAAK
405	Linker Amino Acid Sequence	EAAAKEAAK
406	Linker Amino Acid Sequence	EAAAK
407	Linker Amino Acid Sequence	AEAAAKEAAAKEAAAKEAAKALEAEAAAKEAAAKE AAAK EAAKA
408	Linker Amino Acid Sequence	PAPAP
409	Linker Amino Acid Sequence	AEAAAKEAAKA
410	Linker Amino Acid Sequence	VSQTSKLTRAETVFPDV
411	Linker Amino Acid Sequence	PLGLWA
412	Linker Amino Acid Sequence	RVLAEA
413	Linker Amino Acid Sequence	EDVVCCSMSY
414	Linker Amino Acid Sequence	GGIEGRGS
415	Linker Amino Acid Sequence	TRHRQPRGWE
416	Linker Amino Acid Sequence	AGNRVRRSVG
417	Linker Amino Acid Sequence	RRRRRRRRR
418	Linker Amino Acid Sequence	GFLG
419	Linker Amino Acid Sequence	GGGGS LVPRGSGGGGS

420	Linker Amino Acid Sequence	APAPAPAPAPAPAPAPAPAPAPAPAPAPAPAPAP
421	Linker Amino Acid Sequence	APAPAPAPAPAPAPAPAPAPAPAPAPAPAPAPAP
422	Linker Amino Acid Sequence	APAPAPAPAPAPAPAPAPAPAPAPAPAPAPAPAP
423	Linker Amino Acid Sequence	APAPAPAPAPAPAPAPAPAPAPAPAPAPAPAPAP
424	Linker Amino Acid Sequence	APAPAPAPAPAPAPAPAPAPAPAPAPAPAPAPAP
425	Linker Amino Acid Sequence	APAPAPAPAPAPAPAPAPAPAPAPAPAPAPAPAP
426	Linker Amino Acid Sequence	APAPAPAPAPAPAPAPAPAPAPAPAPAPAPAPAP
427	Linker Amino Acid Sequence	APAPAPAPAPAPAPAPAPAPAPAPAPAPAPAPAP
428	Linker Amino Acid Sequence	APAPAPAPAPAPAPAPAPAPAPAPAPAPAPAPAP
429	Linker Amino Acid Sequence	APAPAPAPAPAPAPAPAPAPAPAPAPAPAPAPAP
430	Linker Amino Acid Sequence	APAPAPAPAPAPAPAPAPAPAPAPAPAPAPAPAP
431	Linker Amino Acid Sequence	APAPAPAPAPAPAPAPAPAPAPAPAPAPAPAPAP
432	Linker Amino Acid Sequence	APAPAPAPAPAPAPAPAPAPAPAPAPAPAPAPAP
433	CD8 β 1 Nucleic Acid Sequence, codon optimized	ATGCGCCCGAGACTGTGGCTTCTGCTCGCCGCGCAAC TGACTGTCCTGCACGGAAACAGCGTGCTGCAGCAGAC ACCGGCCTACATCAAAGTGCAGACCAACAAGATGGTC ATGCTGTCCTGCGAGGCCAAGATTTCCCTCTCCAACAT GCGGATCTATTGGTTGCGGCAGAGACAGGCGCCTTCC TCGGACTCCCACCATGAGTTCTTGCCCTGTGGGACTC CGCCAAGGGAACATTACGGCGAAGAAGTGGAACA GGAGAAGATCGCCGTGTTTCGCGATGCCTCCCGCTTT

		ATACTGAATCTGACCTCCGTGAAGCCCGAAGATAGCG GGATCTACTTTTGCATGATTGTGGGCTCACCCGAAGT ACCTTCGGGAAGGGCACTCAGCTGAGCGTGGTGGACT TCCTCCCCACTACCGCCCAACCCACTAAGAAGTCAAC CCTGAAGAAGCGGGTTTGCAGACTCCCACGGCCGGAA ACGCAGAAGGGTCCGCTGTGTTCCCCGATCACCTGG GGCTCCTTGTGGCTGGAGTGCTGGTCCTTCTGGTGTCC CTTGGCGTCGCCATTACCTCTGCTGCCGGAGAAGGA GGGCCAGACTGAGGTTTCATGAAGCAGCCTCAGGGAG AGGGGATCAGTGGCACTTTCGTGCCACAATGCCTCCA TGGCTACTATTCCAACACCACCACCTCGCAAAAGCTG CTGAACCCCTGGATCCTGAAAACC
434	CD8 α 1 Nucleic Acid Sequence, codon optimized	ATGGCGCTTCCCGTGACCGCACTCCTGTTGCCCTTGC CCTGCTGTTGCACGCCGCACGACCTTCCCAATTCCGG GTGTCCCCTCTGGATCGCACCTGGAACCTCGGGGAAA CGGTGGAGCTCAAGTGTCAAGTCCTCCTGTCTGAACCC GACCAGCGGATGCAGCTGGCTGTTCCAGCCGAGAGGA GCTGCCGCCTCACCCACCTTCCTCCTGTACTTGAGCCA GAACAAGCCGAAGGCCGCTGAGGGTCTGGACACCCA GCGCTTCTCGGGCAAACGGCTGGGAGACACTTTTGTG CTGACTCTCTCCGACTTCCGGCGGGAGAACGAGGGCT ACTACTTCTGCTCTGCGCTCTCCAATTCAATCATGTAC TTCTCACACTTCGTGCCGGTGTTCCTGCCTGCCAAGCC CACCACTACTCCGGCACCCAGACCTCCAACCTCCCGCT CCCACCATCGCGTCCCAACCCCTTTTCGTGCGCCCTGA AGCGTGTCGGCCTGCTGCTGGAGGAGCCGTGCATACC CGCGGTCTGGACTTCGCGTGCGACATCTACATTTGGG CCCCTTTGGCTGGCACCTGTGGAGTGCTGCTCCTGTCC CTTGTGATCACCTGTACTGCAACCACCGGAATAGGC GGAGAGTCTGCAAGTGTCCGCGGCCTGTCGTGAAGTC AGGAGATAAGCCGAGCCTGTCCGCACGCTACGTG
435	m1CD8 α Nucleic Acid Sequence, codon optimized	ATGGCGCTTCCCGTGACCGCACTCCTGTTGCCCTTGC CCTGCTGTTGCACGCCGCACGACCTTCCCAATTCCGG GTGTCCCCTCTGGATCGCACCTGGAACCTCGGGGAAA

		CGGTGGAGCTCAAGTGTCAAGTCCTCCTGTCTCGAACCC GACCAGCGGATGCAGCTGGCTGTTCCAGCCGAGAGGA GCTGCCGCCTCACCCACCTTCCTCCTGTACTTGAGCCA GAACAAGCCGAAGGCCGCTGAGGGTCTGGACACCCA GCGCTTCTCGGGCAAACGGCTGGGAGACACTTTTGTG CTGACTCTCTCCGACTTCCGGCGGGAGAACGAGGGCT ACTACTTCTGCTCTGCGCTCTCCAATTCAATCATGTAC TTCTCACACTTCGTGCCGGTGTTCCTGCCTGCCAGCGT GGTGGACTTCCTCCCCACTACCGCCCAACCCACTAAG AAGTCAACCCTGAAGAAGCGGGTTTGCAGACTCCCAC GGCCGGAACGCAGAAGGGTCCGCTGTGTTCCCCGAT CTACATTGGGGCCCCTTTGGCTGGCACCTGTGGAGTGC TGCTCCTGTCCCTTGTGATCACCTGTACTGCAACCAC CGGAATAGGCGGAGAGTCTGCAAGTGTCCGCGGCCTG TCGTGAAGTCAGGAGATAAGCCGAGCCTGTCCGCACG CTACGTG
436	Full Wild Type IL15 (“wtIL-15” or “wtIL15”) Nucleic Acid Sequence (codon optimized)	ATGAGAATTCGAAACCACATTTGAGAAGTATTTCCA TCCAGTGCTACTTGTGTTTACTTCTAAACAGTCATTTT CTAAGTGAAGCTGGCATTTCATGTCTTCATTTTGGGCTG TTTCAGTGCAGGGCTTCCTAAAACAGAAGCCAACTGG GTGAACGTGATCTCCGACCTGAAGAAGATTGAAGATC TGATCCAGTCCATGCACATTGACGCCACCCCTTTACACC GAGTCAGATGTGCATCCGAGCTGCAAGGTCACCGCGA TGAAGTGTTTCTGCTGGAAGTCCAAGTCATCAGCCTC GAATCCGGCGACGCTTCAATTCACGACACTGTGGAGA ACTTGATCATTCTGGCCAACAACCTCGCTGTCGTCCAAT GGAAACGTGACCGAGTCCGGGTGCAAAGAGTGCGAA GAACTCGAGGAAAAGAACATCAAGGAGTTCCTGCAG TCCTTCGTGCACATCGTGCAGATGTTTATCAACACTAG C
437	Hepatitis B Virus (HBV) Post- Transcriptional Regulatory	TAAACAGGCCTATTGATTGGAAAGTTTGTCAACGAAT TGTGGGTCTTTTGGGGTTTGCTGCCCTTTTACGCAAT GTGGATATCCTGCTTTAATGCCTTTATATGCATGTATA CAAGCAAAACAGGCTTTTACTTTCTCGCCAACTTACA

Element Nucleic Acid Sequence (HPRE)	AGGCCTTTCTCAGTAAACAGTATATGACCCTTTACCCC GTTGCTCGGCAACGGCCTGGTCTGTGCCAAGTGTGTTG CTGACGCAACCCCCACTGGTTGGGGCTTGGCCATAGG CCATCAGCGCATGCGTGGAACCTTTGTGTCTCCTCTGC CGATCCATACTGCGGAACTCCTAGCCGCTTGTTTTGCT CGCAGCAGGTCTGGAGCAAACCTCATCGGGACCGACA ATTCTGTCTGACTCTCCCGCAAGTATACATCGTTTCCA TGGCTGCTAGGCTGTGCTGCCAACTGGATCCTGCGCG GGACGTCCTTTGTTTACGTCCCGTCGGCGCTGAATCCC GCGGACGACCCCTCCCGGGGCGCTTGGGGCTCTACC GCCCCGTTCTCCGTCTGCCGTACCGTCCGACCACGGG GCGCACCTCTCTTTACGCGGACTCCCCGTCTGTGCCTT CTCATCTGCCGGACCGTGTGCACTTCGCTTCACCTCTG CACGTCGCATGGAGACCACCGTGAACGCCACCGGAA CCTGCCCAAGGTCTTGCATAAGAGGACTCTTGGACTT TCAGCAATGTC
Linker Amino Acid Sequence	LE
Kozak Sequence	GCCACC
Kozak Sequence	ACCATGG

[00584] The constructs in Table 2A and in Table 2B each may be assemblages of the individual components described in Table 3. The inventors found that the combination, order, and inclusion of transcription enhancers from Table 3 as described in Table 2A provided unexpected improvements in transfection efficiency, expression levels, and induction of cytotoxic T-cell activities, *e.g.*, IL-12 secretion, IFN- γ secretion, TNF- α secretion, granzyme A secretion, MIP-1a secretion, IP-10 secretion, granzyme B secretion, and any combination thereof.

Tumor Associated Antigens (TAA)

[00585] In the MHC class I dependent immune reaction, peptides not only have to be able to bind to certain MHC class I molecules expressed by tumor cells, they subsequently also have to be recognized by T cells bearing specific T cell receptors (TCR).

[00586] For proteins to be recognized by T-lymphocytes as tumor-specific or -associated antigens, and to be used in a therapy, particular prerequisites must be fulfilled. The antigen

should be expressed mainly by tumor cells and not, or in comparably small amounts, by normal healthy tissues. In embodiments the peptide may be over-presented by tumor cells as compared to normal healthy tissues. It is furthermore desirable that the respective antigen is not only present in a type of tumor, but also in high concentrations (*e.g.*, copy numbers of the respective peptide per cell). Tumor-specific and tumor-associated antigens are often derived from proteins directly involved in transformation of a normal cell to a tumor cell due to their function, *e.g.*, in cell cycle control or suppression of apoptosis. Additionally, downstream targets of the proteins directly causative for a transformation may be up-regulated and thus may be indirectly tumor-associated. Such indirect tumor-associated antigens may also be targets of a vaccination approach. Singh-Jasuja *et al.* Cancer Immunol. Immunother. 53 (2004): 187-195. Epitopes are present in the amino acid sequence of the antigen, making the peptide an "immunogenic peptide", and being derived from a tumor associated antigen, leads to a T-cell-response, both *in vitro* and *in vivo*.

[00587] Any peptide able to bind an MHC molecule may function as a T-cell epitope. For the induction of a T-cell-response, the TAA must be presented a T cell having a corresponding TCR and the host must not have immunological tolerance for this particular epitope. Exemplary Tumor Associated Antigens (TAA) that may be used with the CD8 polypeptides described herein are disclosed herein.

Table 4. TAA Peptide sequences

SEQ ID NO:	Amino Acid Sequence	SEQ ID NO:	Amino Acid Sequence	SEQ ID NO:	Amino Acid Sequence
98	YLYDSETKNA	151	LLWGHPRVALA	204	SLLNQPKAV
99	HLMDQPLSV	152	VLDGKVAVV	205	KMSELQTYV
100	GLLKKINSV	153	GLLGKVTSV	206	ALLEQTGDMSL
101	FLVDGSSAL	154	KMISAIPTL	207	VIKGLEEITV
102	FLFDGSANLV	155	GLLETTGLLAT	208	KQFEGTVEI
103	FLYKIIDEL	156	TLNTLDINL	209	KLQEEIPVL
104	FILDSAETTTL	157	VIKGLEEI	210	GLAEFQENV
105	SVDVSPPKV	158	YLEDGFAYV	211	NVAEIVIH
106	VADKIHSV	159	KIWEELSVLEV	212	ALAGIVTNV
107	IVDDLITNL	160	LLIPFTIFM	213	NLLIDDKGTIKL
108	GLLEELVTV	161	ISLDEVAVSL	214	VLMQDSRLYL
109	TLDGAAVNQV	162	KISDFGLATV	215	KVLEHVVRV

110	SVLEKEIYSI	163	KLIGNIHGNEV	216	LLWGNLPEI
111	LLDPKTIFL	164	ILLSVLHQL	217	SLMEKNQSL
112	YTFSGDVQL	165	LDSEALLTL	218	KLLAVIHEL
113	YLMDDFSSL	166	VLQENSSDYQSNL	219	ALGDKFLLRV
114	KVWSDVTPL	167	HLLGEGAFAQV	220	FLMKNSDLYGA
115	LLWGHPRVALA	168	SLVENIHVL	221	KLIDHQGLYL
116	KIWEELSVLEV	169	YTFSGDVQL	222	GPGIFPPPPQP
117	LLIPFTIFM	170	SLSEKSPEV	223	ALNESLVEC
118	FLIENLLAA	171	AMFPDTIPRV	224	GLAALAVHL
119	LLWGHPRVALA	172	FLIENLLAA	225	LLLEAVWHL
120	FLLEREQLL	173	FTAEFLEKV	226	SIIEYLPTL
121	SLAETIFIV	174	ALYGNVQQV	227	TLHDQVHLL
122	TLLEGISRA	175	LFQSRIAGV	228	SLLMWITQC
123	KIQEILTQV	176	ILAEPIYIRV	229	FLLDKPQDLSI
124	VIFEGEPMYL	177	FLLEREQLL	230	YLLDMPLWYL
125	SLFESLEYL	178	LLLPLELSLA	231	GLLDCPIFL
126	SLLNQPKAV	179	SLAETIFIV	232	VLIEYNFSI
127	GLAEFQENV	180	AILNVDEKNQV	233	TLYNPERTITV
128	KLLAVIHEL	181	RLFEEVLGV	234	AVPPPPSSV
129	TLHDQVHLL	182	YLDEVAFML	235	KLQEELNKV
130	TLYNPERTITV	183	KLIDEDEPLFL	236	KLMDPGSLPPL
131	KLQEKIQEL	184	KLFEKSTGL	237	ALIVSLPYL
132	SVLEKEIYSI	185	SLLEVNEASSV	238	FLLDGSANV
133	RVIDDSL VGV	186	GVYDGREHTV	239	ALDPSGNQLI
134	VLFGELPAL	187	GLYPVTLVGV	240	ILIKHLVKV
135	GLVDIMVHL	188	ALLSSVAEA	241	VLLDTILQL
136	FLNAIETAL	189	TLLEGISRA	242	HLIAEIHTA
137	ALLQALMEL	190	SLIEESEEL	243	SMNGGVFAV
138	ALSSSQAEV	191	ALYVQAPTV	244	MLAEKLLQA
139	SLITGQDLLSV	192	KLIYKDLVSV	245	YMLDIFHEV
140	QLIEKNWLL	193	ILQDGQFLV	246	ALWLPTDSATV
141	LLDPKTIFL	194	SLLDYEYSI	247	GLASRILDA
142	RLHDENILL	195	LLGDSSFFL	248	ALSVLRLAL
143	YTFSGDVQL	196	VIFEGEPMYL	249	SYVKVLHHL

144	GLPSATTTV	197	ALSYILPYL	250	VYLPKIPSW
145	GLLPSAESIKL	198	FLFVDPELV	251	NYEDHFPLL
146	KTASINQNV	199	SEWGSPHAAVP	252	VYIAELEKI
147	SLLQHLIGL	200	ALSELERVL	253	VHFEDTGKTLLF
148	YLMDDFSSL	201	SLFESLEYL	254	VLSPFILTL
149	LMYPYIYHV	202	KVLEYVIKV	255	HLLEGSVG
150	KVWSDVTPL	203	VLLNEILEQV		

EXAMPLE 2

CD8 α molecules and membrane-bound IL-15 Polypeptides

CD8 polypeptides

[00588] CD8 α homodimer (CD8 $\alpha\alpha$) may be composed of two α subunits held together by two disulfide bonds at the stalk regions. FIG. 1 shows a CD8 α polypeptide, e.g., SEQ ID NO: 258 (CD8 α 1), that includes five domains: (1) one signal peptide (from -21 to -1), e.g., SEQ ID NO: 6, (2) one Ig-like domain-1 (from 1 to 115), e.g., SEQ ID NO: 1, (3) one stalk region (from 116 to 160), e.g., SEQ ID NO: 260, (4) one transmembrane (TM) domain (from 161-188), e.g., SEQ ID NO: 3, and (5) one cytoplasmic tail (Cyto) comprising a *lck*-binding motif (from 189 to 214), e.g., SEQ ID NO: 4. Another example of CD8 α subunit, e.g., CD8 α 2 (SEQ ID NO: 259), differs from CD8 α 1 at position 112, at which CD8 α 2 contains a cysteine (C), whereas CD8 α 1 contains a tyrosine (Y).

Modified CD8 polypeptides

[00589] Different from CD8 α polypeptide, e.g., CD8 α 1 (SEQ ID NO: 258) and CD8 α 2 (SEQ ID NO: 259), a modified CD8 α polypeptide, e.g., m1CD8 α (SEQ ID NO: 7) and m2CD8 α (SEQ ID NO: 262), may contain additional regions, such as sequence stretches from a CD8 β polypeptide. In embodiments SEQ ID NO: 2 or variants thereof are used with a CD8 α polypeptide. In other embodiments, a portion of a CD8 α polypeptide, e.g., SEQ ID NO: 260, is removed or not included in modified CD8 polypeptides described herein. FIG. 2 shows a sequence alignment between CD8 α 1 (SEQ ID NO: 258) and m1CD8 α (SEQ ID NO: 7). FIG. 3 shows a sequence alignment between CD8 α 2 (SEQ ID NO: 259) and m2CD8 α (SEQ ID NO: 262), in which the cysteine substitution is indicated by an arrow. The stalk regions are shown within the boxes. CD8 α polypeptide CD8 α 1 (SEQ ID NO: 258) may be encoded by SEQ ID NO: 434. Modified CD8 α polypeptide m1CD8 α (SEQ ID NO: 7) may be encoded by SEQ ID NO: 435.

[00590] Modified CD8 expressing cells showed improved functionality in terms of cytotoxicity and cytokine response as compared to original CD8 expressing T cells transduced with the TCR.

Membrane-bound IL-15 polypeptides

[00591] Membrane-bound IL-15 may comprise, for example, an IL-15/IL-15R α fusion polypeptide and/or an IL-15R α /IL-15 fusion polypeptide. One or more linkers may be disposed between IL-15 and IL-15R α or between IL-15R α and IL-15. An exemplary IL-15/IL-15R α fusion polypeptide comprising one or more linker is depicted in FIG. 67A. An exemplary IL-15R α /IL-15 fusion polypeptide comprising one or more linker is depicted in FIG. 67B. The IL-15 polypeptide in FIGS. 67A and 67B may be immature wild type, immature mutated, mature wild type, or mature mutated. The IL-15R α polypeptide in FIGS. 67A and 67B may be immature wild type, immature mutated, mature wild type, or mature mutated. In embodiments the IL-15 polypeptide in FIG. 67A and FIG. 67B is mature and may or may not be mutated, and the IL-15R α polypeptide in FIG. 67A and FIG. 67B is mature and may or may not be mutated. In embodiments the IL-15 polypeptide in FIG. 67A and FIG. 67B is mature and may or may not be mutated, and the IL-15R α polypeptide in FIG. 67A and FIG. 67B is mature and mutated. Although a linker is depicted in FIG. 67A and FIG. 67B, a linker is optional and a mbIL-15 polypeptides not comprising a linker are also contemplated.

[00592] An IL-15/IL-15R α fusion polypeptide and/or an IL-15R α /IL-15 fusion polypeptide may also comprise one or more signal peptide, such as, but not limited to, a signal peptide derived from IgE, such as the signal peptide of SEQ ID NO: 367, encoded by SEQ ID NO: 368. An exemplary IL-15/IL-15R α fusion polypeptide comprising one or more linker and at least one signal peptide is depicted in FIG. 68A. An exemplary 15R α /IL-15 fusion polypeptide comprising at least one linker and at least one signal peptide is depicted in FIG. 68B. The IL-15 polypeptide in FIGS. 68A and 68B may be immature wild type, immature mutated, mature wild type, or mature mutated. The IL-15R α polypeptide in FIGS. 68A and 68B may be immature wild type, immature mutated, mature wild type, or mature mutated. In embodiments the IL-15 polypeptide in FIG. 68A and FIG. 68B is mature and may or may not be mutated, and the IL-15R α polypeptide in FIG. 68A and FIG. 68B is mature and may or may not be mutated. In embodiments the IL-15 polypeptide in FIG. 68A and FIG. 68B is mature and may or may not be mutated, and the IL-15R α polypeptide in FIG. 68A and FIG. 68B is mature and mutated. Although a linker is depicted in FIG. 68A and FIG. 68B, a linker is optional and a mbIL-15 polypeptides not comprising a linker are also contemplated.

[00593] An IL-15/IL-15R α fusion polypeptide may comprise or consist of appropriate amino acid sequences identified herein. An IL-15/IL-15R α fusion polypeptide may be encoded by one or more nucleic acids comprising or consisting of appropriate nucleic acid sequences identified herein.

EXAMPLE 3

Lentiviral viral vectors

[00594] The lentiviral vectors used herein contain several elements that enhance vector function, including a central polypurine tract (cPPT) for improved replication and nuclear import, a promoter from the murine stem cell virus (MSCV) (SEQ ID NO: 263), which lessens vector silencing in some cell types, a woodchuck hepatitis virus posttranscriptional responsive element (WPRE) (SEQ ID NO: 264) for improved transcriptional termination, and the backbone was a deleted 3'-LTR self-inactivating (SIN) vector design that improves safety, sustained gene expression and anti-silencing properties. Yang *et al. Gene Therapy* (2008) 15, 1411–1423.

[00595] In embodiments vectors, constructs, or sequences described herein comprise mutated forms of WPRE. In embodiments sequences or vectors described herein comprise mutations in WPRE version 1, e.g., WPREmut1 (SEQ ID NO: 256), or WPRE version 2, e.g., WPREmut2 (SEQ ID NO: 257). Construct #9 and Construct #9b represent two LV production batches with the same construct containing SEQ ID NO: 257 as WPREmut2, with the difference between Construct #9 and Construct #9b being the titer consistent with Table 4. In embodiments WPRE mutants comprise at most one mutation, at most two mutations, at most three mutations, at least four mutations, or at most five mutations. In embodiments vectors, constructs, or sequences described herein do not comprise WPRE. In an aspect, WPRE sequences described in U.S. 2021/0285011, the content of which is incorporated by reference in its entirety, may be used together with vectors, sequences, or constructs described herein.

[00596] In embodiments vectors, constructs, or sequences described herein do not include an X protein promoter. The WPRE mutants described herein do not express an X protein. WPRE promotes accumulation of mRNA, theorized to promote export of mRNA from nucleosome to cytoplasm to promote translation of the transgene mRNA.

[00597] To obtain optimal co-expression levels of TCR $\alpha\beta$, mCD8 α (e.g., m1CD8 α (SEQ ID NO: 7) (which may be encoded by SEQ ID NO: 435) and m2CD8 α (SEQ ID NO: 262)) and CD8 β (e.g., any one of CD8 β 1-7 (SEQ ID NO: 8-14)), and a membrane-bound IL-15 (e.g., an IL-15/IL-15R α fusion protein (e.g., any one of SEQ ID NO: 317, 319, 321, 323, 325, 327, 329, 331, 333, 335, 337, 339, 341, 343, 345, 347, 349, 351, 353, or 355; any one of SEQ ID NO: 317, 319, 321, 323, 325, 327, 329, 331, 333, 337, 339, 341, 343, 345, 347, 349, 351, or 353; or any one of SEQ ID NO: 317, 321, 325, 327, 329, 331, 333, 337, 341, 345, 347, 349, 351, or 353)) in

the transduced CD4⁺ T cells, CD8⁺ T cells, and/or $\gamma\delta$ T cells, lentiviral vectors with various designs may be generated. T cells may be transduced with two separate lentiviral vectors (2-in-1), e.g., one expressing TCR α and TCR β and the other expressing mCD8 α and CD8 β , for co-expression of TCR $\alpha\beta$ and CD8 $\alpha\beta$ heterodimer, or one expressing TCR α and TCR β and the other expressing mCD8 α for co-expression of TCR $\alpha\beta$ and mCD8 α homodimer. Alternatively, T cells may be transduced with a single lentiviral vector (4-in-1) co-expressing TCR α , TCR β , mCD8 α , and CD8 β for co-expression of TCR $\alpha\beta$ and CD8 $\alpha\beta$ heterodimer. In the 4-in-1 vector, the nucleotides encoding TCR α chain, TCR β chain, mCD8 α chain, and CD8 β chain may be shuffled in various orders, e.g., from 5' to 3' direction, TCR α -TCR β -mCD8 α -CD8 β , TCR α -TCR β -CD8 β -mCD8 α , TCR β -TCR α -mCD8 α -CD8 β , TCR β -TCR α -CD8 β -mCD8 α , mCD8 α -CD8 β -TCR α -TCR β , mCD8 α -CD8 β -TCR β -TCR α , CD8 β -mCD8 α -TCR α -TCR β , and CD8 β -mCD8 α -TCR β -TCR α . Various 4-in-1 vectors, thus generated, may be used to transduce CD4⁺ T cells, CD8⁺ T cells, and/or $\gamma\delta$ T cells, followed by measuring TCR $\alpha\beta$ /mCD8 α /CD8 β co-expression levels of the transduced cells using techniques known in the art, e.g., flow cytometry. Similarly, T cells may be transduced with a single lentiviral vector (3-in-1) co-expressing TCR α , TCR β , and mCD8 α (e.g., m1CD8 α and m2CD8 α) for co-expression of TCR $\alpha\beta$ and mCD8 α homodimer. In the 3-in-1 vector, the nucleotides encoding TCR α chain, TCR β chain, mCD8 α chain may be shuffled in various orders, e.g., TCR α -TCR β -mCD8 α , TCR β -TCR α -mCD8 α , mCD8 α -TCR α -TCR β , and mCD8 α -TCR β -TCR α . Various 3-in-1 vectors, thus generated, may be used to transduce CD4⁺ T cells, CD8⁺ T cells, and/or $\gamma\delta$ T cells, followed by measuring TCR $\alpha\beta$ /mCD8 α co-expression levels of the transduced cells using techniques known in the art. Vectors co-expressing any combination of TCR α , TCR β , mCD8 α , CD8 β , and/or membrane-bound IL-15, e.g., IL-15/IL-15R α fusion protein, in any order, may be generated, and such vectors may be used to transduce CD4⁺ T cells, CD8⁺ T cells, and/or $\gamma\delta$ T cells, followed by measuring TCR $\alpha\beta$ /mCD8 α /membrane-bound IL-15 co-expression levels of the transduced cells using techniques known in the art..

[00598] To generate lentiviral vectors co-expressing TCR $\alpha\beta$ and mCD8 α and/or CD8 β , a nucleotide encoding furin-linker (GSG or SGSG (SEQ ID NO: 266))-2A peptide may be positioned between TCR α chain and TCR β chain, between mCD8 α chain and CD8 β chain, between a TCR chain and a CD8 chain, and/or between a CD8 or TCR chain and a membrane-bound IL-15 to enable highly efficient gene expression. The 2A peptide may be selected from P2A (SEQ ID NO: 93), T2A (SEQ ID NO: 94), E2A (SEQ ID NO: 95), or F2A (SEQ ID NO: 96).

[00599] Lentiviral viral vectors may also contain post-transcriptional regulatory element (PRE), such as WPRE (SEQ ID NO: 264), WPREmut1 (SEQ ID NO: 256), or WPREmut2 (SEQ

ID NO: 257), which may function to enhance the expression of one or more transgene by increasing both nuclear and cytoplasmic mRNA levels. One or more regulatory elements including mouse RNA transport element (RTE), the constitutive transport element (CTE) of the simian retrovirus type 1 (SRV-1), and the 5' untranslated region of the human heat shock protein 70 (Hsp70 5'UTR) may also be used and/or in combination with WPRE to increase transgene expression. The WPREmut1 and WPREmut2 do not express an X protein, but still act to enhance translation of the transgene mRNA.

[00600] Lentiviral vectors may be pseudotyped with RD114TR (for example, SEQ ID NO: 97), which is a chimeric glycoprotein comprising an extracellular and transmembrane domain of feline endogenous virus (RD114) directly or indirectly fused to cytoplasmic tail (TR) of murine leukemia virus. Other viral envelop proteins, such as VSV-G env, MLV 4070A env, RD114 env, chimeric envelope protein RD114pro, baculovirus GP64 env, or GALV env, or derivatives thereof, may also be used. RD114TR variants comprising at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 98%, at least about 99%, or about 100% identity to SEQ ID NO: 97 also provided for.

[00601] For example, FIG. 4 shows exemplary vectors, which include two 4-in-1 vectors, e.g., Constructs #10 and #2, co-expressing TCR (TCR α chain and TCR β chain), CD8 α , and CD8 β ; three 3-in-1 vectors expressing TCR and CD8 α , e.g., Constructs #1 and #9, two 3-in-1 vectors expressing TCR and m1CD8 α (SEQ ID NO: 7), e.g., Constructs #11 and #12, and Construct #8 expressing TCR only. To improve transcriptional termination, wild type WPRE (WPRE) (SEQ ID NO: 264) is included in Constructs #1, #2, and #8; WPREmut (SEQ ID NO: 257) is included in Constructs #9, #10, #11, and #12.

[00602] As another example, FIG. 70 depicts exemplary vectors that are provided in embodiments. For example, Constructs K-U depicted in FIG. 70 are provided in embodiments. The TCRs in FIG. 70 may be, for example, TCR β directly or indirectly fused to TCR α with or without a linker and/or other elements therebetween or TCR α directly or indirectly fused to TCR β with or without a linker and/or other elements therebetween. The IL-15 polypeptides in FIG. 70 may be immature wild type, immature mutated, mature wild type, or mature mutated. The IL-15R α polypeptides in FIG. 70 may be immature wild type, immature mutated, mature wild type, or mature mutated. In embodiments the IL-15 polypeptides in FIG. 70 are mature and may or may not be mutated, and the IL-15R α polypeptides in FIG. 70 are mature and may or may not be mutated. In embodiments the IL-15 polypeptides in FIG. 70 are mature and may or may not be mutated, and the IL-15R α polypeptides in FIG. 70 are mature and mutated. The CD8 α , CD8 β , and TCR polypeptides in FIG. 70 may independently be as described herein

and/or may independently be modified or unmodified. In embodiments CD8 α may comprise or consist of CD8 α 1 (SEQ ID NO: 258, which may be encoded by SEQ ID NO: 434). In embodiments CD8 α may comprise or consist of m1CD8 α (SEQ ID NO: 7, which may be encoded by SEQ ID NO: 435). In embodiments CD8 β may comprise or consist of CD8 β 1 (SEQ ID NO: 8, which may be encoded by SEQ ID NO: 433). In embodiments, constructs express an IL-15 polypeptide fused to a WPRE element, a linker and a CD25 or CD28 transmembrane domain as defined herein.

[00603] In embodiments, the nucleic acid encoding mbIL-15 in any of Constructs K-T may be selected from nucleic acid sequences encoding (i) SEQ ID NO: 307 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto, directly or indirectly fused to an N terminus of SEQ ID NO: 309 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto, with or without a linker therebetween; (ii) SEQ ID NO: 307 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto, directly or indirectly fused to an N terminus of SEQ ID NO: 311 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto, with or without a linker therebetween; (iii) SEQ ID NO: 307 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto, directly or indirectly fused to an N terminus of SEQ ID NO: 313 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto, with or without a linker therebetween; or (iv) SEQ ID NO: 307 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto, directly or indirectly fused to an N terminus of SEQ ID NO: 315 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto, with or without a linker therebetween; (v) any of SEQ ID NO: 317, 319, 321, 323, 325, 327, 329, 331, 333, 335, 337, 339, 341, 343, 345, 347, 349, 351, 353, or 355; or (vi) a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to any of SEQ ID NO: 317, 319, 321, 323, 325, 327, 329, 331, 333, 335, 337, 339, 341, 343, 345, 347, 349, 351, 353, or 355. In embodiments, a sequence encoding a signal peptide may be directly or indirectly fused to the 5' end of a nucleic acid encoding any of SEQ ID NO: 307, 317, 319, 321, 323, 325, 327, 329, 331, 333, or 335 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 307, 317, 319, 321, 323, 325, 327, 329, 331, 333, or 335. In embodiments the signal

peptide may be derived from an IgE polypeptide. In embodiments the signal peptide derived from an IgE polypeptide may comprise SEQ ID NO: 367 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto. However, in embodiments an IL-15/IL-15R α fusion polypeptide does not comprise or consist of (i) SEQ ID NO: 307 directly or indirectly fused to an N terminus of SEQ ID NO: 309 with a linker therebetween, with or without SEQ ID NO: 367 directly or indirectly fused to an N terminus of SEQ ID NO: 307, (ii) sequences having about 95% or more sequence identity to SEQ ID NO: 307 directly or indirectly fused to an N terminus of SEQ ID NO: 309 with a linker therebetween with or without SEQ ID NO: 367 directly or indirectly fused to an N terminus of SEQ ID NO: 307; (iii) SEQ ID NO: 335 or SEQ ID NO: 355; or (iv) sequences having about 95% or more sequence identity to SEQ ID NO: 335 or SEQ ID NO: 355.

[00604] In embodiments, the nucleic acid encoding mbIL-15 in any of Constructs K-U may be selected from nucleic acid sequences encoding (i) SEQ ID NO: 307 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto, directly or indirectly fused to an N terminus of SEQ ID NO: 311 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto, with or without a linker therebetween; (ii) SEQ ID NO: 307 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto, directly or indirectly fused to an N terminus of SEQ ID NO: 313 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto, with or without a linker therebetween; or (iii) SEQ ID NO: 307 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto, directly or indirectly fused to an N terminus of SEQ ID NO: 315 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto, with or without a linker therebetween; (iv) any of SEQ ID NO: 317, 319, 321, 323, 325, 327, 329, 331, 333, 337, 339, 341, 343, 345, 347, 349, 351, or 353; or (vi) a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to any of SEQ ID NO: 317, 319, 321, 323, 325, 327, 329, 331, 333, 337, 339, 341, 343, 345, 347, 349, 351, or 353. In embodiments, a sequence encoding a signal peptide may be directly or indirectly fused to the 5' end of a nucleic acid encoding any of SEQ ID NO: 307, 317, 319, 321, 323, 325, 327, 329, 331, or 333 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 307, 317, 319, 321, 323, 325, 327, 329, 331, or 333. In embodiments the signal peptide may be derived from an IgE polypeptide. In embodiments the

signal peptide derived from an IgE polypeptide may comprise SEQ ID NO: 367 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[00605] In embodiments, the nucleic acid encoding mbIL-15 in any of Constructs K-U may be selected from nucleic acid sequences encoding (i) any of SEQ ID NO: 317, 321, 325, 327, 329, 331, 333, 337, 341, 345, 347, 349, 351, or 353 or (ii) a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to any of SEQ ID NO: 317, 321, 325, 327, 329, 331, 333, 337, 341, 345, 347, 349, 351, or 353. In embodiments, a sequence encoding a signal peptide may be directly or indirectly fused to the 5' end of a nucleic acid encoding any of SEQ ID NO: 317, 321, 325, 327, 329, 331, or 333, or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 317, 321, 325, 327, 329, 331, or 333. In embodiments the signal peptide may be derived from an IgE polypeptide. In embodiments the signal peptide derived from an IgE polypeptide may comprise SEQ ID NO: 367 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[00606] In embodiments, the nucleic acid encoding mbIL-15 in any of Constructs K-U may be selected from nucleic acid sequences comprising or consisting of (i) SEQ ID NO: 308 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto, directly or indirectly fused to a 5' end of SEQ ID NO: 310 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto, with or without a linker therebetween; (ii) SEQ ID NO: 308 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto, directly or indirectly fused to 5' end of SEQ ID NO: 312 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto, with or without a linker therebetween; (iii) SEQ ID NO: 308 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto, directly or indirectly fused to 5' end of SEQ ID NO: 314 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto, with or without a linker therebetween; or (iv) SEQ ID NO: 308 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto, directly or indirectly fused to 5' end of SEQ ID NO: 316 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto, with or without a linker therebetween; (v) any of

SEQ ID NO: 318, 320, 322, 324, 326, 328, 330, 332, 334, 336, 338, 340, 342, 344, 346, 348, 350, 352, 354, or 356; or (vi) a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to any of SEQ ID NO: 318, 320, 322, 324, 326, 328, 330, 332, 334, 336, 338, 340, 342, 344, 346, 348, 350, 352, 354, or 356. In embodiments, a sequence encoding a signal peptide may be directly or indirectly fused to the 5' end of a nucleic acid encoding any of SEQ ID NO: 308, 318, 320, 322, 324, 326, 328, 330, 332, 334, or 336 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 308, 318, 320, 322, 324, 326, 328, 330, 332, 334, or 336. In embodiments the signal peptide may be derived from an IgE polypeptide. In embodiments the nucleic acid encoding the signal peptide derived from an IgE polypeptide may comprise or consist of SEQ ID NO: 368 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto. However, In embodiments an IL-15/IL-15R α fusion polypeptide does not comprise or consist of (i) SEQ ID NO: 308 directly or indirectly fused to a 5' end of SEQ ID NO: 310 with a linker therebetween, with or without SEQ ID NO: 368 directly or indirectly fused to an N terminus of SEQ ID NO: 308, (ii) sequences having about 80%, about 85%, about 90%, or about 95% or more sequence identity to SEQ ID NO: 308 directly or indirectly fused to an N terminus of SEQ ID NO: 310 with a linker therebetween with or without SEQ ID NO: 368 directly or indirectly fused to an N terminus of SEQ ID NO: 308; (iii) SEQ ID NO: 336 or SEQ ID NO: 356; or (iv) sequences having about 80%, about 85%, about 90%, or about 95% or more sequence identity to SEQ ID NO: 336 or SEQ ID NO: 356.

[00607] In embodiments, the nucleic acid encoding mbIL-15 in any of Constructs K-U may be selected from nucleic acid sequences comprising or consisting of (i) SEQ ID NO: 308 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto, directly or indirectly fused to 5' end of SEQ ID NO: 312 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto, with or without a linker therebetween; (ii) SEQ ID NO: 308 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto, directly or indirectly fused to 5' end of SEQ ID NO: 314 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto, with or without a linker therebetween; or (iii) SEQ ID NO: 308 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto, directly or indirectly fused to 5' end of SEQ ID NO: 316 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100%

identical thereto, with or without a linker therebetween; (iv) any of SEQ ID NO: 318, 320, 322, 324, 326, 328, 330, 332, 334, 338, 340, 342, 344, 346, 348, 350, 352, or 354; or (vi) a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to any of SEQ ID NO: 318, 320, 322, 324, 326, 328, 330, 332, 334, 338, 340, 342, 344, 346, 348, 350, 352, or 354. In embodiments, a sequence encoding a signal peptide may be directly or indirectly fused to the 5' end of a nucleic acid encoding any of SEQ ID NO: 308, 318, 320, 322, 324, 326, 328, 330, 332, or 334 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 308, 318, 320, 322, 324, 326, 328, 330, 332, or 334. In embodiments the signal peptide may be derived from an IgE polypeptide. In embodiments the nucleic acid encoding the signal peptide derived from an IgE polypeptide may comprise or consist of SEQ ID NO: 368 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[00608] In embodiments, the nucleic acid encoding mbIL-15 in any of Constructs K-U may be selected from nucleic acid sequences comprising or consisting of (i) any of SEQ ID NO: 318, 322, 326, 328, 330, 332, 334, 338, 342, 346, 348, 350, 352, or 354 or (ii) a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to any of SEQ ID NO: 318, 322, 326, 328, 330, 332, 334, 338, 342, 346, 348, 350, 352, or 354. In embodiments, a sequence encoding a signal peptide may be directly or indirectly fused to the 5' end of a nucleic acid encoding any of SEQ ID NO: 318, 322, 326, 328, 330, 332, or 334, or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 318, 322, 326, 328, 330, 332, or 334. In embodiments the signal peptide may be derived from an IgE polypeptide. In embodiments the nucleic acid encoding the signal peptide derived from an IgE polypeptide may comprise or consist of SEQ ID NO: 368 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

[00609] Further exemplary constructs (Constructs #13-#19 and #21-#25) are described in Table 2 above. In particular, Constructs #13, #14, and #16 are 4-in-1 constructs co-expressing TCR, CD8 α , and CD8 β 3 with various combinations of signal peptides (SEQ ID NO: 6 [WT CD8 α signal peptide]; SEQ ID NO: 293 [WT CD8 β signal peptide]; and SEQ ID NO: 294 [S19 signal peptide]) and differing element order. Constructs #15 and #17 are 4-in-1 constructs co-expressing TCR, CD8 α , and CD8 β 5. Construct #15 comprises the WT CD8 α signal peptide (SEQ ID NO: 6) and WT CD8 β signal peptide (SEQ ID NO: 293), whereas Construct #17 comprises the S19 signal peptide (SEQ ID NO: 294) at the N-terminal end of both CD8 α and CD8 β 5. Construct #21 is a 4-in-1 constructs co-expressing TCR, CD8 α , and CD8 β 2 comprising

WT CD8 α signal peptide (SEQ ID NO: 6) and WT CD8 β signal peptide (SEQ ID NO: 293). Construct #18 is a variant of Construct #10 in which the WT signal peptides for CD8 α and CD8 β 1 (SEQ ID NOs: 6 and 293, respectively) were replaced with S19 signal peptide (SEQ ID NO: 294). Construct #19 is a variant of Construct #11 in which the WT CD8 α signal peptide (SEQ ID NO: 6) was replaced with the S19 signal peptide (SEQ ID NO: 294). Construct #22 is a variant of Construct #11 in which the CD4 transmembrane and intracellular domains are directly or indirectly fused to the C-terminus of the CD8 β stalk sequence in place of the CD8 α transmembrane and intracellular domains. Construct #25 is a variant of Construct #22 in which the CD8 β stalk sequence (SEQ ID NO: 2) is replaced with the CD8 α stalk sequence (SEQ ID NO: 260).

Further constructs

[00610] Further constructs within the scope of the present invention include constructs #26 – # and co-express TCR, CD8 α , CD8 β and mbIL15 (SEQ ID NO: 438 to 447).

EXAMPLE 4

Vector screening (Constructs #1, #2, #8, #9, #10, #11, and #12)

Viral titers

[00611] FIG. 5A shows viral titer of Constructs #1, #2, #8, #9, #10, #11, and #12. Table 5 shows viral titers and lentiviral P24 ELISA data for Constructs #9, #10, #11, and #12.

Table 5

Constructs #	Titer	Lentiviral P24
9	5.40×10^9	6556
9b	9.80×10^9	16196
10	6.40×10^9	9525
11	1.30×10^{10}	16797
12	1.20×10^{10}	17996

[00612] For construct 12, NCAMfu refers to NCAMFusion protein expressing modified CD8 α extracellular and Neural cell adhesion molecule 1 (CD56) intracellular domain.

[00613] For Table 5, the WPREmut2 portion refers to SEQ ID NO: 257.

T cell manufacturing

Activation

[00614] FIG. 6 shows that, on Day +0, PBMCs (about 9×10^8 cells) obtained from two donors (Donor # 1 and Donor #2) were thawed and rested. Cells were activated in bags (AC290) coated with anti-CD3 and anti-CD28 antibodies in the presence of serum. Activation markers, e.g., CD25, CD69, and human low density lipoprotein receptor (H-LDL-R) are in CD8+ and CD4+ cells, were subsequently measured. FIG. 7A shows that % CD3+CD8+CD25+ cells, % CD3+CD8+CD69+ cells, and % CD3+CD8+H-LDL-R+ cells increase after activation (Post-A) as compared with that before activation (Pre-A). Similarly, FIG. 7B shows that % CD3+CD4+CD25+ cells, % CD3+CD4+CD69+ cells, and % CD3+CD4+H-LDL-R+ cells increase after activation (Post-A) as compared with that before activation (Pre-A). These results support the activation of PBMCs.

Transduction

[00615] FIG. 6 shows that, on Day +1, activated PBMCs were transduced with viral vectors, e.g., Constructs #1, #2, #8, #9, #10, #11, and #12, in G-Rex® 6 well plates at about 5×10^6 cells/well in the absence of serum. The amounts of virus used for transduction are shown in Table 6.

Table 6

Constructs	Virus Volume/ 1×10^6 cells
#9, #10, #11, #12	1.25 μ l, 2.5 μ l, 5 μ l
#1	1.25 μ l
#2	5 μ l
#8 (TCR)	2.5 μ l

Expansion

[00616] FIG. 6 shows that, on Day +2, transduced PBMCs were expanded in the presence of serum. On Day +6, cells were harvested for subsequent analysis, e.g., FACS-Dextramer and vector copy number (VCN) and were cryopreserved. FIG. 8A and 8B show fold expansion on Day +6 of transduced T cell products obtained from Donor #1 and donor #2, respectively. Viabilities of cells is greater than 90% on Day +6.

Characterization of T cell products

[00617] Cell counts, FACS-dextramers, and vector copy numbers (VCN) were determined. Tetramer panels may comprise live/dead cells, CD3, CD8 α , CD8 β , CD4, and peptide/MHC

tetramers, e.g., PRAME-004 (SLLQHLIGL) (SEQ ID NO: 147)/MHC tetramers. FACS analysis was gated on live singlets, followed by CD3+, followed by CD4+CD8+, followed by CD4+CD8+Tetramer(Tet)+ and CD8+Tet+.

[00618] FIGS. 9A, 9B, 9C, and 9D show representative flow plots of cells obtained from Donor #1 indicating % CD8, CD4, and PRAME-004/MHC tetramer (Tet) of cells transduced with Construct #9b, #10, #11, or #12, respectively.

[00619] FIG. 10 shows % CD8+CD4+ cells from Donor #1 (upper panel) and Donor #2 (lower panel) transduced with Construct #1, #2, #8 (TCR), #9, #10, #11, or #12 at 1.25 μ l, 2.5 μ l, or 5 μ l per 1×10^6 cells. These results show that higher % CD8+CD4+ cells were obtained by transduction with vectors expressing CD8 α and TCR with wild type WPRE (Construct #1) and WPREmut2 (Construct #9) than that transduced with Constructs #10, #11, or #12. Construct #8 (TCR only) serves as negative control. FIG. 11 shows % Tet of CD8+CD4+ cells from Donor #1 (upper panel) and Donor #2 (lower panel) transduced with Constructs #1, #2, #8 (TCR), #9, #10, #11, and #12 at 1.25 μ l, 2.5 μ l, or 5 μ l per 1×10^6 cells. These results show that % Tet of CD8+CD4+ cells appear comparable among cells transduced with Constructs #9, #10, and #11, and seems greater than that transduced with Construct #12. FACS analysis was gated on live singlets, followed by CD3+, followed by CD4+CD8+, and followed by CD4+CD8+Tet+.

[00620] FIG. 12 shows Tet MFI of CD8+CD4+Tet+ cells from Donor #1 (upper panel) and Donor #2 (lower panel) transduced with Construct #1, #2, #8 (TCR), #9, #10, #11, or #12 at 1.25 μ l, 2.5 μ l, or 5 μ l per 1×10^6 cells. These results show that tetramer MFI on CD4+CD8+Tet+ varies among donors. FIG. 13 shows CD8 α MFI of CD8+CD4+Tet+ cells from Donor #1 (upper panel) and Donor #2 (lower panel) transduced with Construct #1, #2, #8 (TCR), #9, #10, #11, or #12 at 1.25 μ l, 2.5 μ l, or 5 μ l per 1×10^6 cells. These results show higher CD8 α MFI in cells transduced with vectors expressing CD8 α and TCR with wild type WPRE (Construct #1) and WPREmut2 (Construct #9) than that transduced with the other constructs. Transduction volume of 5 μ l/ 10^6 appears to yield better results than 1.25 μ l/ 10^6 and 2.5 μ l/ 10^6 . FACS analysis was gated on live singlets, followed by CD3+, followed by CD4+CD8+, followed by CD4+CD8+Tet+, and followed by Tet MFI/CD8 α MFI.

[00621] FIG. 14 shows CD8 frequencies (% CD8+CD4- of CD3+) in cells from Donor #1 (upper panel) and Donor #2 (lower panel) transduced with Construct #1, #2, #8 (TCR), #9, #10, #11, or #12 at 1.25 μ l, 2.5 μ l, or 5 μ l per 1×10^6 cells. These results show no difference in the CD8 frequencies among the constructs. Non-transduction (NT) serves as negative control. FIG. 15 shows % CD8+Tet+ (of CD3+) cells from Donor #1 (upper panel) and Donor #2 (lower panel) transduced with Construct #1, #2, #8 (TCR), #9, #10, #11, or #12 at 1.25 μ l, 2.5 μ l, or 5 μ l per 1×10^6 cells. These results show higher frequencies of CD8+Tet+ (of CD3+) in cells

transduced with Constructs #9, #11, and #12 than that transduced with Construct #10. FACS analysis was gated on live singlets, followed by CD3+, followed by CD8+CD4-, and followed by CD8+Tet+.

[00622] FIG. 16 shows Tet MFI of CD8+Tet+ cells from Donor #1 (upper panel) and Donor #2 (lower panel) transduced with Construct #1, #2, #8 (TCR), #9, #10, #11, or #12 at 1.25 μ l, 2.5 μ l, or 5 μ l per 1×10^6 cells. These results show tetramer MFI of CD8+tet+ cells varies among donors. FIG. 17 shows CD8 α MFI of CD8+Tet+ cells from Donor #1 (upper panel) and Donor #2 (lower panel) transduced with Construct #1, #2, #8 (TCR), #9, #10, #11, or #12 at 1.25 μ l, 2.5 μ l, or 5 μ l per 1×10^6 cells. These results show that CD8 α MFI of CD8+Tet+ are comparable among cells transduced with different constructs. FACS analysis was gated on live singlets, followed by CD3+, followed by CD4+CD8+, followed by CD4+CD8+Tet+, and followed by Tet MFI/CD8 α MFI.

[00623] FIG. 18 shows % Tet+ of CD3+ cells from Donor #1 (upper panel) and Donor #2 (lower panel) transduced with Construct #1, #2, #8 (TCR), #9, #10, #11, or #12 at 1.25 μ l, 2.5 μ l, or 5 μ l per 1×10^6 cells. These results show higher frequencies of CD3+Tet+ in cells transduced with Construct #9 or #11 than that transduced with Construct #10 or #12. It appears more % Tet+CD3+ cells in cells transduced with Construct #10 (WPREmut2) than that transduced with Construct #2 (wild type WPRE) at 5 μ l per 1×10^6 cells. FACS analysis was gated on live singlets, followed by CD3+, followed by CD3+, and followed by Tet+.

[00624] FIG. 19 (upper panel) shows vector copy number (VCN) of cells from Donor #1 transduced with Construct #1, #2, #8 (TCR), #9, #10, #11, or #12 at 1.25 μ l, 2.5 μ l, or 5 μ l per 1×10^6 cells. These results show higher VCN for cells transduced with Constructs #11 or #12 (may be due to higher titers) than that transduced with Construct #9 or #10. FIG. 19 (lower panel) shows CD3+Tet+/VCN of cells from Donor #1 transduced with Construct #1, #2, #8 (TCR), #9, #10, #11, or #12 at 1.25 μ l, 2.5 μ l, or 5 μ l per 1×10^6 cells. These results show higher CD3+Tet+/VCN in cells transduced with Construct #9 than that transduced with Construct #10, #11, or #12.

[00625] In sum, these results show (1) higher % CD8+CD4+ cells obtained by transducing cells with vectors expressing CD8 α and TCR with wild type WPRE (Construct #1) and WPREmut2 (Construct #9) than that transduced with Construct #10, #11 or #12; (2) % CD8+CD4+Tet+ cells was comparable among cells transduced with different constructs; (3) dose dependent increase in % tetramer, e.g., 5 μ l per 1×10^6 cells showed better results than 1.25 μ l and 2.5 μ l per 1×10^6 cells; (4) % CD8+ cells comparable among cells transduced with different constructs; (5) higher frequencies of CD8+Tet+ in cells transduced with Construct #9, #11, or #12 than that transduced with Construct #10; (6) higher frequencies of CD3+Tet+ in cells

transduced with Construct #9 or #11 than that transduced with Construct #10 or #12; (7) higher VCN in cells transduced with Construct #11 or #12 than that transduced with Construct #9 or #10; and (8) higher CD3+tet+/VCN in cells transduced with Construct #9 than that transduced with Construct #10, #11, or #12.

[00626] T cell products transduced with viral vector expressing a transgenic TCR and modified CD8 co-receptor showed superior cytotoxicity and increased cytokine production against target positive cell lines.

EXAMPLE 5

Tumor Death Assay

[00627] FIG. 20A-C depicts data showing that constructs (#10, #11, & #12) are comparable to TCR-only in mediating cytotoxicity against target positive cells lines expressing antigen at different levels (UACC257 at 1081 copies per cell and A375 at 50 copies per cell).

Table 7

Tumor Cell Line	Antigen Positivity
UACC257	High
A375	Low
MCF7	Negative

[00628] Construct #9 loses tumor control over time against the low target antigen expressing A375 cell line.

EXAMPLE 6

IFN γ Secretion Assay

[00629] IFN γ secretion was measured in UACC257 and A375 cells lines. IFN γ secretion in response in UACC257 cell line was comparable among constructs. However, in the A375 cell line, Construct #10 showed higher IFN γ secretion than other constructs. IFN γ quantified in the supernatants from Incucyte plates. FIG. 21A-B.

[00630] FIG. 22 depicts an exemplary experiment design to assess Dendritic Cell (DC) maturation and cytokine secretion by PBMC-derived T cell products in response to exposure to target positive tumor cell lines UACC257 and A375.

[00631] IFN γ secretion in response to A375 increases in the presence of immature DC (iDCs). In the tri-cocultures with iDCs, IFN γ secretion is higher in Construct #10 compared to the other constructs. However, comparing Construct #9 with Construct #11 expressing wild type and modified CD8 coreceptor sequences respectively, T cells transduced with #11 induced stronger

cytokine response measured as IFN γ quantified in the culture supernatants of three-way cocultures using donor D600115, E:T:iDC::1:1/10:1/4. FIG. 23A-B.

[00632] IFN γ secretion in response to A375 increases in the presence of iDCs. In the tri-cocultures with iDCs, IFN γ secretion was higher in Construct #10 compared to the other constructs. IFN γ quantified in the supernatants from DC cocultures D150081, E:T:iDC::1:1/10:1/4. FIG. 24A-B

[00633] IFN γ secretion in response to UACC257 increases in the presence of iDCs. In the tri-cocultures with iDCs, IFN γ secretion is higher in Construct #10 compared to the other constructs. However, comparing Construct #9 with Construct #11 expressing wild type and modified CD8 coreceptor sequences respectively, T cells transduced with Construct #11 induced stronger cytokine response measured as IFN γ quantified in the culture supernatants of three-way cocultures using donor D600115, E:T:iDC::1:1/10:1/4. FIG. 25A-B. These results demonstrate that T cell products co-expressing a transgenic TCR and CD8 co-receptor ($\alpha\beta$ heterodimer or modified CD8 α homodimer) are able to license DCs in the microenvironment through antigen cross presentation and therefore hold the potential to mount a stronger anti-tumor response and modulate the tumor microenvironment.

EXAMPLE 7

Vector screening (Constructs #13-#21)

Viral titers

[00634] FIG. 5B shows viral titer of Constructs #10, #10n (new batch), #11, #11n (new batch), #13 - #21, and TCR only as a control.

T cell manufacturing

Activation

[00635] FIG. 26 shows that, on Day +0, PBMCs obtained from two HLA-A02+ donors (Donor # 1 and Donor #2) were thawed and rested. Cells were activated in bags (AC290) coated with anti-CD3 and anti-CD28 antibodies in the absence of serum. Activation markers, e.g., CD25, CD69, and human low density lipoprotein receptor (H-LDL-R) are in CD8+ and CD4+ cells, were subsequently measured. FIG. 27A shows that % CD3+CD8+CD25+ cells, % CD3+CD8+CD69+ cells, and % CD3+CD8+H-LDL-R+ cells increase after activation (Post-A) as compared with that before activation (Pre-A). Similarly, FIG. 27B shows that % CD3+CD4+CD25+ cells, % CD3+CD4+CD69+ cells, and % CD3+CD4+H-LDL-R+ cells increase after activation (Post-A) as compared with that before activation (Pre-A). These results support the activation of PBMCs.

Transduction

[00636] FIG. 26 shows that, on Day +1, activated PBMCs were transduced with viral vectors, e.g., Constructs #8, #10, #10n, #11, #11n, and #13-#21, in G-Rex® 24-well plates at about 2×10^6 cells/well in the absence of serum. The amounts of virus used for transduction are shown in Table 8.

Table 8

Constructs	Virus Volume/ 1×10^6 cells
#10n, #11n, #13-#21	0.3 μ l, 1.1 μ l, 3.3 μ l, 10 μ l, 30 μ l
#8 (TCR), #10	2.5 μ l
#11	1.25 μ l
NT	-

Expansion

[00637] FIG. 26 shows that, on Day +2, transduced PBMCs were expanded in the absence of serum. On Day +6, cells were harvested for subsequent analysis, e.g., FACS-Tetramer and vector copy number (VCN) and were cryopreserved. FIG. 28 shows fold expansion on Day +6 of transduced T cell products. Viabilities of cells is greater than 90% on Day +6.

Characterization of T cell products

[00638] Cell counts, FACS-dextramers, and vector copy numbers (VCN) were determined. Tetramer panels may comprise live/dead cells, CD3, CD8 α , CD8 β , CD4, and peptide/MHC tetramers, e.g., PRAME-004 (SLLQHLIGL) (SEQ ID NO: 147)/MHC tetramers. FACS analysis was gated on live singlets, followed by CD3+, followed by CD4+CD8+, followed by CD4+CD8+Tetramer(Tet)+ and CD8+Tet+.

[00639] FIG. 29A and FIG. 29B shows % CD8+CD4+ cells transduced with Construct #10, #10n, #11, #13-#21 at 0.3 μ l, 1.1 μ l, 3.3 μ l, 10 μ l or 30 μ l per 1×10^6 cells. These results show comparable frequencies of CD8+CD4+ cells obtained by transduction with all vectors tested. Construct #8 (TCR only) serves as negative control. FIG. 30A and FIG. 30B shows % Tet of CD8+CD4+ cells from transduced with Construct #10, #10n, #11, #13-#21 at 0.3 μ l, 1.1 μ l, 3.3 μ l, 10 μ l or 30 μ l per 1×10^6 cells. These results show that there was a trend towards higher frequencies of CD4+CD8+tet+ in CD8 β 1 isoforms (Constructs #10 and #18) compared to CD8 β 3 isoforms (Construct #16) and CD8 β 5 isoforms (Constructs # 15 and #17). FACS analysis was gated on live singlets, followed by CD3+, followed by CD4+CD8+, and followed by CD4+CD8+Tet+.

[00640] FIG. 31A and FIG. 31B shows Tet MFI of CD8+CD4+Tet+ cells from transduced with Construct #10, #10n, #11, #13-#21 at 0.3 μ l, 1.1 μ l, 3.3 μ l, 10 μ l or 30 μ l per 1×10^6 cells. These results show a trend towards higher tetramer MFI on CD4+CD8+Tet+ population in CD8 β 1 isoforms (Constructs #10 and #18) compared to CD8 β 3 isoforms (Construct #16) and CD8 β 5 isoforms (Constructs # 15 and #17).

[00641] FIG. 32A and FIG. 32B show CD8 frequencies (% CD8+CD4- of CD3+) in cells transduced with Construct #10, #10n, #11, #13-#21 at 0.3 μ l, 1.1 μ l, 3.3 μ l, 10 μ l or 30 μ l per 1×10^6 cells. These results show no difference in the CD8 frequencies among the constructs. FIG. 33A and FIG. 33B shows % CD8+Tet+ (of CD3+) cells transduced with Construct #10, #10n, #11, #13-#21 at 0.3 μ l, 1.1 μ l, 3.3 μ l, 10 μ l or 30 μ l per 1×10^6 cells. These results show slightly higher frequencies of CD8+Tet+ (of CD3+) in cells transduced with Construct #10 than those transduced with the other constructs. FACS analysis was gated on live singlets, followed by CD3+, followed by CD8+CD4-, and followed by Tet+.

[00642] FIG. 34A and FIG. 34B shows Tet MFI of CD8+Tet+ cells transduced with Construct #10, #10n, #11, #13-#21 at 0.3 μ l, 1.1 μ l, 3.3 μ l, 10 μ l or 30 μ l per 1×10^6 cells. These results show tetramer MFI of CD8+tet+ cells was comparable among CD8 β 1 (Constructs #18 and #10), CD8 β 5 (Constructs # 15 and #17), and CD8 β 3 (Construct #16) isoforms, while Construct #21 expressed lower tetramer MFI.

[00643] FIG. 35A and FIG. 35B shows % Tet+ of CD3+ cells transduced with Construct #10, #10n, #11, #13-#21 at 0.3 μ l, 1.1 μ l, 3.3 μ l, 10 μ l or 30 μ l per 1×10^6 cells. These results show higher frequencies of CD3+Tet+ in cells transduced with Construct #10 (CD8 β 1) compared to those transduced with CD8 β 3 (Construct #16) and CD8 β 5 (Constructs #15 and #17). FACS analysis was gated on live singlets, followed by CD3+, and followed by Tet+.

[00644] FIG. 36A and FIG. 36B shows vector copy number (VCN) of cells transduced with Construct #10, #10n, #11, #13-#21 at 0.3 μ l, 1.1 μ l, 3.3 μ l, 10 μ l or 30 μ l per 1×10^6 cells. These results show comparable ability of all constructs to integrate and express CD8/TCR genes.

[00645] In sum, these results show (1) viral vectors with CD8 β 1, CD8 β 3 and CD8 β 5 isoforms had good transducing titers; (2) all constructs were capable of successful manufacturing (e.g., high viability, fold expansions in the range of 6-12); (3) frequencies of CD3+tet+ among CD8 β isoforms: CD8 β 1 (Construct #10) was greater than CD8 β 3 (Construct #16) and CD8 β 5 (Constructs #15 and #17), with Construct #21 showing the lowest values; (4) frequency of CD3+tet+ in Constructs #11 and #19 (m1CD8 α (SEQ ID NO: 7)) showed the highest values; and (5) saturation in %CD3+tet+, %CD8+tet+ and %CD4+CD8+tet+ observed at 10 μ l/e6. Optimal vector dose ranges between 3.3-10 μ l/e6 for all constructs.

EXAMPLE 8**Mid-Scale Vector screening (Constructs #13-#19)**

T cell manufacturing

Activation/Transduction

[00646] FIG. 37 shows that, on Day +0, PBMCs obtained from four HLA-A02+ donors were thawed and rested. Cells were activated in bags (AC290) coated with anti-CD3 and anti-CD28 antibodies in the absence of serum. On Day +1, activated PBMCs were transduced with viral vectors, *e.g.*, Constructs #8, #10n, #11n, and #13-#19, in G-Rex® 6-well plates at about 7×10^6 cells/well in the absence of serum. The amounts of virus used for transduction are shown in Table 9.

Table 9

Constructs	Virus Volume/ 1×10^6 cells
#13-19	2.5 μ l and 5 μ l
#10n and #11n	2.5 μ l and 5 μ l
#8 (TCR)	2.5 μ l
NT	-

Expansion

[00647] FIG. 37 shows that, on Day +2, transduced PBMCs were expanded in the absence of serum. On Day +7, cells were harvested for subsequent analysis, *e.g.*, FACS-Tetramer and vector copy number (VCN) and were cryopreserved. Fold expansion on Day +7 was comparable for all constructs (approximately 30-fold expansion). Viabilities of cells is greater than 90% on Day +7.

Characterization of T cell products

[00648] Cell counts, FACS-dextramers, and vector copy numbers (VCN) were determined. Tetramer panels may comprise live/dead cells, CD3, CD8 α , CD8 β , CD4, and peptide/MHC tetramers, *e.g.*, PRAME-004 (SLLQHLIGL) (SEQ ID NO: 147)/MHC tetramers. FACS analysis was gated on live singlets, followed by CD3+, followed by CD4+CD8+, followed by CD4+CD8+Tetramer(Tet)+ and CD8+Tet+.

[00649] Similar to results described in Example 6, comparable frequencies of CD8+CD4+ cells were obtained by transduction with Construct #10n, #11n, #13-#19 at 2.5 μ l or 5.0 μ l per 1×10^6 cells. Construct #8 (TCR only) serves as negative control. FIG. 38 shows % Tet of CD8+CD4+ cells transduced with Construct #10n, #11n, #13-#19 at 2.5 μ l or 5.0 μ l per 1×10^6 cells. Similar to results described in Example 6, these results show that there was a trend towards

higher frequencies of CD4+CD8+tet+ in CD8 β 1 isoforms (Construct #10n) compared to CD8 β 3 isoforms (Constructs #13, #14, #16) and CD8 β 5 isoforms (Constructs #15 and #17). FACS analysis was gated on live singlets, followed by CD3+, followed by CD4+CD8+, and followed by Tet+.

[00650] FIG. 39 shows Tet MFI of CD8+CD4+Tet+ cells from transduced with Construct #10n, #11n, #13-#19 at 2.5 μ l or 5.0 μ l per 1×10^6 cells. These results show higher tetramer MFIs on CD4+CD8+Tet+ population in CD8 β 1 isoforms (Construct #10n) compared to CD8 β 3 isoforms (Construct #13) and CD8 β 5 isoforms (Constructs #15 and #17).

[00651] Similar to results described in Example 6, results show no difference in the CD8 frequencies (% CD8+CD4- of CD3+) in cells transduced with Construct #10n, #11n, #13-#19 at 2.5 μ l or 5.0 μ l per 1×10^6 cells among the constructs (data not shown). Comparable frequencies of CD8+Tet+ (of CD3+) in cells transduced with Construct #10n, #11n, #13-#19 at 2.5 μ l or 5.0 μ l per 1×10^6 cells (data not shown). FACS analysis was gated on live singlets, followed by CD3+, followed by CD8+CD4-, and followed by Tet+.

[00652] FIG. 40 shows Tet MFI of CD8+Tet+ cells transduced with Construct #10n, #11n, #13-#19 at 2.5 μ l or 5.0 μ l per 1×10^6 cells. These results show tetramer MFI of CD8+tet+ cells was comparable among CD8 β 1 (Constructs #18 and #10) and CD8 β 5 (Construct #15) isoforms, while CD8 β 3 (Constructs #13, #14, and #16) isoforms expressed lower tetramer MFI.

[00653] FIG. 41 shows % Tet+ of CD3+ cells transduced with Construct #10n, #11n, #13-#19 at 2.5 μ l or 5.0 μ l per 1×10^6 cells. These results show slightly higher frequencies of CD3+Tet+ in cells transduced with Construct #10 (CD8 β 1) compared to those transduced with CD8 β 3 (Constructs #13, #14, and #16) and CD8 β 5 (Construct #15). FACS analysis was gated on live singlets, followed by CD3+, and followed by Tet+. Slightly higher total CD3+tet+ cell counts were observed in PBMC transduced with Construct #10 (CD8 β 1) compared to those transduced with CD8 β 3 (Constructs #13, #14, and #16) and CD8 β 5 (Construct #15) (data not shown).

[00654] FIG. 42 shows vector copy number (VCN) of cells transduced with Construct #10n, #11n, #13-#19 at 2.5 μ l or 5.0 μ l per 1×10^6 cells. These results show vector copies per cell remained below 5 in PBMC product derived using each individual construct at vector dose of 2.5 μ l or 5.0 μ l per 1×10^6 cells.

[00655] FIG. 43 shows the % T cell subsets in cells transduced with Construct #10, #11, #13, and #15 for each donor. Construct #8 (TCR only) and non-transduced cells were used as controls. These results show that TCR-only condition has slightly more naïve cells compared to the other constructs, consistent with lower fold-expansion. FIG. 44A and FIG. 44B shows % T cell subsets in cells transduced with Construct #10, #11, #13, and #15 for each donor. Construct #8 (TCR only) and non-transduced cells were used as controls. FACS analysis was gated on

CD4+CD8+ for FIG. 44A and on CD4-CD8+TCR+ for FIG. 44B. These results show donor-to-donor variability between frequencies of T cell memory subsets but little difference in the frequencies of T_{naive} and T_{cm} between constructs.

[00656] In sum, these results show (1) viability and fold expansions were comparable among all constructs at day 7; (2) slightly higher frequency of CD3+tet+ observed in CD8β1 (Construct #10) compared to CD8β3 (Constructs # 13, #14, and #16) and CD8β5 (Constructs #15 and #17); (3) vector copies per cell < 5 for majority of the constructs at 2.5-5ul/10⁶ dose; and (4) donor-to-donor variability between frequencies of T cell memory subsets but generally, Construct #10 has less naïve but more T_{cm} cells than the other β isoform constructs.

EXAMPLE 9

Tumor Death Assay – Constructs #10, #11, #13 & #15

[00657] FIG. 45A and 45B depicts data showing that Constructs #13 and #10 are comparable to TCR-only in mediating cytotoxicity against UACC257 target positive cells lines expressing high levels of antigen (1081 copies per cell). Construct # 15 was also effective but slower in killing compared to Constructs #13 and #10. The effector:target ratio used to generate these results was 4:1. Similar results were obtained with a 2:1 effector:target ratio (data not shown).

EXAMPLE 10

IFNγ Secretion Assay – Constructs #10, #11, #13 & #15

[00658] IFNγ secretion was measured in the UACC257 cells line. FIG. 46 shows IFNγ secretion in response in UACC257 cell line was higher with Construct #13 compared to Construct #10. IFNγ quantified in the supernatants from Incucyte plates. The effector:target ratio used to generate these results was 4:1. Similar results were obtained with a 2:1 effector:target ratio (data not shown).

EXAMPLE 11

ICI Marker Expression – Constructs #10, #11, #13 & #15

[00659] ICI marker frequency (2B4, 41BB, LAG3, PD-1, TIGIT, TIM3, CD39+CD69+, and CD39-CD69-) was measured. FIG. 47 shows Construct #15 has higher expression of LAG3, PD-1, and TIGIT compared to other constructs, followed by Construct #10.

EXAMPLE 12

Cytokine Expression – Constructs #10, #11, #13 & #15

[00660] Expression of various cytokines was measured in UACC257 cells co-cultured at a 4:1 E:T ratio with PBMC transduced with Constructs #10, #11, #13, and #15. FIG. 48A – 48G show

increased expression of IFN γ , IL-2, and TNF α with CD4+CD8+ cells transduced with construct #10 (WT signal peptide, CD8 β 1) compared to other constructs. FACS analysis was gated on CD3+CD4+CD8+ cells against UACC257, 4:1 E:T. FIG. 49A-49G show increased expression of IFN γ , IL-2, MIP-1 β , and TNF α with CD4-CD8+ cells transduced with construct #10 (WT signal peptide, CD8 β 1) compared to other constructs. FACS analysis was gated on CD3+CD4-CD8+ cells against UACC257, 4:1 E:T. FIG. 50A-50G show increased expression of IL-2 and TNF α with CD3+TCR+ cells transduced with construct #10 (WT signal peptide, CD8 β 1) compared to other constructs. MIP-1 β expression is highest in Construct #11 (similar results when gated on CD4+CD8+ cells). FACS analysis was gated on CD3+TCR+ cells against UACC257, 4:1 E:T.

[00661] Expression of various cytokines was measured in A375 cells co-cultured at a 4:1 E:T ratio with PBMC transduced with Constructs #10, #11, #13, and #15. FIG. 51A-51C show results from FACS analysis gated on CD4+CD8+ cells against A375, 4:1 E:T. FIG. 52A-52C show results from FACS analysis gated on CD4-CD8+ cells against A375, 4:1 E:T. FIG. 53A-53C show results from FACS analysis gated on CD3+TCR+ cells against A375, 4:1 E:T. Overall, results were more variable when cells are co-cultured with A375+RFP, but similar trends are observed compared to activation by UACC257+RFP.

EXAMPLE 13

Large-Scale Vector screening (Constructs #10, #11, #13, #16, #18, #19)

T cell manufacturing

Activation/Transduction

[00662] FIG. 54 shows that, on Day +0, PBMCs obtained from three HLA-A02+ donors were thawed and rested. Cells were activated in bags (AC290) coated with anti-CD3 and anti-CD28 antibodies in the absence of serum. On Day +1, activated PBMCs were transduced with viral vectors, *e.g.*, Constructs #8, #10n, #11n, #13, #16, #18, and #19 in G-Rex® 100 cell culture vessels at about 5×10^7 cells/vessel in the absence of serum. The amounts of virus used for transduction are shown in Table 10.

Table 10

Constructs	Virus Volume/1 x 10 ⁶ cells
#13, #16, #18, #10n	5 μ l
#19 and #11n	2.5 μ l
#8 (TCR)	2.5 μ l
NT	-

Expansion

[00663] FIG. 54 shows that, on Day +2, transduced PBMCs were expanded in the absence of serum. On Day +7, cells were harvested for subsequent analysis, e.g., FACS-Tetramer and vector copy number (VCN) and were cryopreserved. Fold expansion on Day +7 was comparable for all constructs (approximately 30-fold expansion). Viabilities of cells is greater than 90% on Day +7.

Characterization of T cell products

[00664] Cell counts, FACS-dextramers, and vector copy numbers (VCN) were determined. Tetramer panels may comprise live/dead cells, CD3, CD8 α , CD8 β , CD4, and peptide/MHC tetramers, e.g., PRAME-004 (SLLQHLIGL) (SEQ ID NO: 147)/MHC tetramers. FACS analysis was gated on live singlets, followed by CD3+, followed by CD4+CD8+, followed by CD4+CD8+Tetramer(Tet)+ and CD8+Tet+.

[00665] Tumor death assays and cytokine expression in the presence and absence of autologous immature dendritic cells was also measured.

[00666] The results were consistent with the prior examples and are summarized in Table 11.

Table 11

	Parameters	Construct #10	Construct #13	Construct #11	Construct #19	TCR only Construct #8
Manufacturing	Viabilities	>90%	>90%	>90%	>90%	>90%
	Fold Expansion d7	28.7 $\pm$ 11%	28.6 $\pm$ 11%	31.6 $\pm$ 13%	29.6 $\pm$ 13%	30.1 $\pm$ 11%
	Transgene expression (%CD3+Tet+), mean $\pm$ SD	46.9 $\pm$ 12%	42 $\pm$ 9.8%	41 $\pm$ 12%	48.2 $\pm$ 14%	22.8 $\pm$ 8%
	Vector Copy Number	3.3 $\pm$ 0.6%	2.6 $\pm$ 0.7%	2.0 $\pm$ 0.8%	3.1 $\pm$ 1.8%	1.7 $\pm$ 0.7%
Functionality	Multiple rounds of killing with UACC	+++	+++	+++	+++	+++
	Cytokine secretion (24h, with UACC); IFN-g, TNF-a, IL-2	+++	+++	++	++	++
	Cytokine secretion; CD4+CD8+TCR+ (16h, UACC); ICS	+++	+++	+	+	+/-

	DC licensing assay (PBM product)					
	IL-12, TNF-α & IL-6	+++	+++	+	+	+
	3D Spheroid Assay	+++	N/A	+++	N/A	++

EXAMPLE 14**DC licensing by CD4 cells expressing Constructs of the Present Disclosure**

[00667] FIG. 59 shows a scheme of determining the levels of cytokine secretion by dendritic cells (DC) in the presence of PBMCs transduced with constructs of the present disclosure and in the presence of target cells, e.g., UACC257 cells. Briefly, Day 0, PBMCs (n = 3) were thawed and rested, followed by monocyte isolation and autologous immature DCs (iDC) generation in the presence of IL-4 and GM-CSF; Day 2 and Day 4-5, DC were fed in the presence of IL-4 and GM-CSF; Day 6, iDC (+DC) were co-cultured with PBMC transduced with Construct #13, #16, #10n, #18, #11n, or #19 (Effector) and UACC257 cells (Target) at a ratio of Effector : Target : iDC = 1 : 1/10 : 1/4 or without iDC (-DC), PBMCs transduced with TCR only, PBMCs without transduction (NT), PBMCs treated with iDC and LPS, and iDC only serve as controls; and Day 7 (after co-culturing for 24 hours), supernatants from the co-cultures were harvested, followed by cytokine profiling including, e.g., IL-12, IL-6, and TNF- α , using Multiplex.

[00668] Increased secretion of pro-inflammatory cytokines in tri-cocultures of autologous immature dendritic cells, UACC257 tumor cell line, and CD4⁺ T cell product expressing CD8 $\alpha\beta$ heterodimer and TCR (Construct #10) compared with that expressing CD8 α^* homodimer, in which the stalk region is replaced with CD8 β stalk region, and TCR (Construct #11).

[00669] To determine the ability of CD4⁺ T cells expressing Constructs #10 or #11 to license DC, bulk PBMCs were transduced with Constructs #10 or #11, followed by selection of CD8⁺ and CD4⁺ cells from the product. Tri-cocultures of PBMCs, CD8⁺CD4⁻ selected-product, or CD4⁺CD8⁺ selected-product with UACC257 tumor cell line in the presence or absence of autologous immature dendritic cells (iDCs) for 24 h followed by cytokine quantification of IL-12, TNF- α and IL-6 using Multiplex; iDCs alone or with LPS as controls, N = 4-7, mean $\pm$ SD, P values based on 2way ANOVA.

[00670] In the presence of immature dendritic cells (iDCs) and UACC257 cells, CD4⁺ T cells expressing Construct #10 (CD4⁺CD8⁺ T cells) performed better by inducing higher levels of IL-12 (FIG. 56), TNF- α (FIG. 57), and IL-6 (FIG. 58) secreted by dendritic cells (DC) than CD4⁺ T cells expressing Construct #11. On the other hand, the levels of IL-12, TNF- α , and IL-6 were comparable between CD8⁺ T cells expressing Constructs #10 and #11 (CD8⁺CD4⁻ T cells).

These results suggest that CD4⁺ T cells expressing CD8 $\alpha\beta$ heterodimer and TCR (Construct #10) may be a better product than CD4⁺ T cells expressing CD8 α * homodimer and TCR (Construct #11) in DC licensing. The negative controls include the cytokine levels obtained (1) in the absence of iDCs (-iDCs), (2) in the presence of non-transduced T cells (NT) + UACC257 cells, and (3) in the presence of T cells transduced with TCR only (TCR) + UACC257 cells. The positive control includes the cytokine levels obtained from iDCs treated with lipopolysaccharide (LPS), which can activate DC.

EXAMPLE 15

Assessment of DC maturation and cytokine secretion by PBMC products in response to UACC257 targets

[00671] FIG. 60 shows IL-12 secretion levels induced by co-culturing PBMCs transduced with constructs of the present disclosure in the presence or absence of iDC and target cells, e.g., UACC257 cells. For example, IL-12 secretion was increased by co-culturing PBMCs transduced with Constructs #10 and 13 in the presence of iDC (+DC) and UACC257, as compared with that by co-culturing PBMCs transduced with TCR only. Increase of IL-12 secretion suggests (1) polarization towards Th1 cell-mediated immunity including TNF- α production (see, FIG. 61), (2) T cell proliferation, (3) IFN- γ production, and (4) cytolytic activity of cytotoxic T lymphocytes (CTLs).

[00672] FIG. 61 shows TNF- α secretion levels induced by co-culturing PBMCs transduced with constructs of the present disclosure in the presence or absence of iDC and target cells, e.g., UACC257 cells. For example, TNF- α secretion was increased by co-culturing PBMCs transduced with Constructs #10 and 13 in the presence of iDC (+DC) and UACC257, as compared with that by co-culturing PBMCs transduced with TCR only.

[00673] The increased IL-6 secretion (in addition to IL-12, TNF- α) may signify dendritic cell maturation, which may be augmented by CD40-CD40L interactions between CD4⁺ T cells and DCs. DC maturation and subsequent cytokine secretion may aid in modulation of the proinflammatory environment.

[00674] FIG. 62 shows IL-6 secretion levels induced by co-culturing PBMCs transduced with constructs of the present disclosure in the presence or absence of iDC and target cells, e.g., UACC257 cells. For example, IL-6 secretion was increased by co-culturing PBMCs transduced with Constructs #10 and 13 in the presence of iDC (+DC) and UACC257, as compared with that by co-culturing PBMCs transduced with TCR only.

[00675] These results show that PBMC products containing CD4⁺ T cells co-expressing transgenic TCR and CD8 co-receptor (CD8 $\alpha\beta$ heterodimer or CD8 α homodimer) may license

DCs in the microenvironment through antigen cross presentation to modulate the tumor microenvironment by, e.g., increasing IL-12, IL-6, and TNF- α secretion.

[00676] Table 12 shows comparison between constructs based on manufacturability and functionality.

Table 12

	Parameters	Construct #10	Construct #13	Construct #11	Construct #19	TCR only
Manufacturability	Viabilities	>90%	>90%	>90%	>90%	>90%
	Fold expansion on Day 7	28.7 $\pm$ 11%	28.6 $\pm$ 11%	31.6 $\pm$ 13%	29.6 $\pm$ 13%	30.1 $\pm$ 11%
	Transgene expression (%CD3+Tet+) mean $\pm$ SD	46.9 $\pm$ 12%	42 $\pm$ 9.8%	41 $\pm$ 12%	48.2 $\pm$ 14%	22.8 $\pm$ 8%
	Vector copy number	3.3 $\pm$ 0.6%	2.6 $\pm$ 0.7%	2.0 $\pm$ 0.8%	3.1 $\pm$ 1.8%	1.7 $\pm$ 0.7%
Functionality	Multiple rounds of killing with UACC257 cells	+++	+++	+++	+++	+++
	Cytokine secretion (24h, with UACC257 cells); IFN- γ , TNF- α , IL-2	+++	+++	++	++	++
	Cytokine secretion; CD4+CD8+TCR+ (16h with UACC257 cells); ICS	+++	+++	+	+	+/-
	DC licensing assay (PBMC product) IL-12, TNF- α , and	+++	+++	+	+	+

	IL-6					
	3D spheroid assay	+++	N/A	+++	N/A	++

Notes: “+++” = best response; “++” = good response; “+” = average response; “+/-” = poor response.

[00677] Table 13 shows construct comparison and ranking (the smaller the number the better).

Table 13

Parameters	Construct #10	Construct #13	Construct #11	Construct #19
Manufacturability	1	1	1	1
Functionality PBMC	1	1	2	2
Functionality CD8	1	1	1	1
Functionality CD4	1	1	3	3
Time delay*	1	1	1	1
Total	5	5	8	8

* Time delay here refers to any delay from, for example, GMP Vector manufacturing or any delay due to incomplete data set, which may add delay in implementation of constructs in clinical trials.

[00678] In sum, while manufacturability in terms of, e.g., viability, fold expansion, transgene expression, and vector copy number, may be equally good, as ranked 1, among cells transduced with Construct # 10, #11, #13, or #19, functionality in terms of, e.g., cell killing, cytokine secretion, DC licensing, and 3D spheroid forming ability, of cells transduced with Construct #10 and #13 may be better, as ranked 1, than those transduced with Construct #11 and #19, as ranked 1-3.

EXAMPLE 16

EC50 Assays

[00679] To determine the efficacy of T cells transduced with constructs of the present disclosure, e.g., Constructs #10 and #11, against target cells, EC50s were determined based on the levels of IFN γ produced by the transduced cells in the presence of PRAME peptide-pulsed T2 cells.

[00680] For example, to compare EC50s of CD4⁺ selected T cells transduced with Construct #10 (CD8 $\alpha\beta$ -TCR), Construct #11 (m1CD8 α -TCR), or Construct #8 (TCR only), CD4⁺ selected products (TCR⁺ normalized) were co-cultured with PRAME peptide-pulsed T2 cells at defined concentrations at E:T ratio of 1:1 for 24 h. IFN γ levels were quantified in the supernatants after 24 h. FIGS. 63A-63C show IFN γ levels produced by the transduced CD4⁺ selected T cells obtained from Donor #1, #2, and #3, respectively. In general, CD4⁺ selected T cells transduced with Construct #10 were more sensitive to PRAME antigen as compared with that transduced with Construct #11 (m1CD8 α TCR⁺ CD4 T cells), as indicated by lower EC50 values (ng/ml) of CD4⁺ selected T cells transduced with Construct #10 than that transduced with Construct #11 (FIG. 63D). No response was observed among TCR⁺ CD4⁺ cells (FIGS. 63A-63D). These results suggest that CD8 $\alpha\beta$ heterodimer may impart increased avidity to CD8 $\alpha\beta$ TCR⁺ CD4⁺ T cells as compared to m1CD8 α homodimer, leading to better efficacy against target cells.

[00681] Similar experiments were performed using PBMC obtained from Donor #1, #3, and #4. Briefly, PBMC products (TCR⁺ non-normalized) were co-cultured with PRAME peptide-pulsed T2 cells at defined concentrations at E:T ratio of 1:1 for 24 h. IFN γ levels were quantified in the supernatants after 24 h. FIGS. 64A-64C show IFN γ levels produced by the transduced PBMC obtained from Donor #4, #1, and #3, respectively. Donor-to-donor variability was observed in the EC50 values. For example, while Donor #3 (FIGS. 64C and 64D) shows lower EC50 of PBMC transduced with Construct #10 as compared with that transduced with TCR only, Donors #1 (FIG. 64B) and #4 (FIG. 64A) show comparable EC50s between Construct #10 and TCR only (FIG. 64D). Thus, the increased avidity and efficacy observed in CD4⁺ selected T cell products expressing TCR and CD8 $\alpha\beta$ heterodimer as compared with that expressing TCR only may be obtained but to lesser extent when using PBMC products.

[00682] To compare EC50s of different T cell products obtained from the same donor, PBMC products, CD8⁺ selected products, and CD4⁺ selected products obtained from a single donor were co-cultured with PRAME peptide-pulsed T2 cells (TCR⁺ normalized) at defined concentrations at E:T ratio of 1:1 for 24 h. IFN γ levels were quantified in the supernatants after 24 h. FIGS. 65A-65C show that IFN γ levels produced by PBMC products (FIG. 65A), CD8⁺ selected products (FIG. 65B), and CD4⁺ selected products (FIG. 65C), respectively. Consistently, EC50 of CD4⁺ selected T cells transduced with Construct #10 was lower than that transduced with Construct #11 or TCR only (FIG. 65C), while EC50s of the transduced PBMC and CD8⁺ selected T cells were comparable between Construct #10 and TCR only transduction. Thus, the increased avidity and efficacy observed in CD4⁺ selected T cell products expressing TCR and CD8 $\alpha\beta$ heterodimer as compared with that expressing TCR and m1CD8 α homodimer

or with that expressing TCR only may be obtained but to lesser extent when using PBMC products or CD8⁺ selected T cell products.

EXAMPLE 17

T Cell Manufacturing

[00683] Activation: Similar to the procedure shown in FIG. 6, on Day +0, PBMCs (about 300 million to 1 billion cells per donor) obtained from donors are thawed and rested. Cells are activated in bags (AC290) coated with anti-CD3 and anti-CD28 antibodies in the presence of serum.

[00684] Transduction: Similar to the procedure shown in FIG. 6, on Day +1, activated PBMCs are transduced with viral vectors, *e.g.*, (i) TCR only (ii) TCR and membrane bound IL-15, (iii) CD8 $\beta\alpha$.TCR, (iv) CD8 $\beta\alpha$.TCR and membrane bound IL-15, (v) m1CD8 α .TCR, or (vi) m1CD8 α .TCR and membrane bound IL-15, in G-Rex® 6 well plates at about 5×10^6 cells/well in the absence of serum. One vector encoding multiple polypeptides may be used to transduce T cells, or multiple vectors may be used. As non-limiting examples, (i) to obtain cells expressing TCR only, Construct #8 may be transduced into cells; (ii) to obtain cells expressing TCR and membrane-bound IL-15, Construct #8 and a vector comprising a nucleic acid encoding membrane-bound IL-15 may be transduced into cells, or Construct O or Construct U may be transduced into cells; (iii) to obtain cells expressing CD8 $\beta\alpha$.TCR, Construct #10 may be transduced into cells; (iv) to obtain cells expressing CD8 $\beta\alpha$.TCR and membrane-bound IL-15, Construct #10 and a vector comprising a nucleic acid encoding membrane-bound IL-15 may be transduced into cells, or Construct L may be transduced into cells; (v) to obtain cells expressing m1CD8 α .TCR, Construct # 11 may be transduced into cells; and/or (vi) to obtain cells expressing m1CD8 α .TCR and membrane-bound IL-15, Construct #10 and a vector comprising a nucleic acid encoding membrane-bound IL-15 may be transduced into cells, or Construct M may be transduced into cells.

[00685] Vector copy number in cells is determined, and other cell characterization is performed.

[00686] Expansion: Similar to the procedure shown in FIG. 6, on Day +2, transduced PBMCs are expanded in the presence of serum. On Day +6 or Day +7, cells are harvested for subsequent analysis, *e.g.*, FACS-Dextramer and vector copy number (VCN) and are cryopreserved.

Characterization of cell products:

[00687] Cell fold expansion and/or viability of transduced and non-transduced cells are determined. Percent of transduced cells expressing each polypeptide of interest is determined.

Cells are characterized through phenotyping (flow-based) and through functional studies. For phenotyping, tetramer, intracellular marker, Tmem, and/or ICS panels may be run to assess different markers of interest. Marker expression may be assessed, as non-limiting examples, in the following populations: CD3+TCR+, CD8+TCR+, CD8+, CD4+CD8+, or CD4+CD8+TCR+. Activation, tetramer frequency and CD4/CD8 frequencies, memory subsets, exhaustion status, and effector molecule expression (via ICS and/or intracellular staining) may be assessed. For cells transduced to express mbIL-15, the following populations may be assessed: CD3+TCR+mbIL-15+, CD8+TCR+mbIL-15+, CD8+mbIL-15+, CD4+CD8+mbIL-15+, and/or CD4+CD8+TCR+mbIL-15+. Additional assays, such as cell trace proliferation assays and/or cell death and apoptosis assays may be performed. Probing for IL-15/IL-15R α fusion polypeptide may be performed using an antibody against IL-15R α .

EXAMPLE 18

Serial Killing Assays

[00688] Transduced and non-transduced cells are cocultured with tumor cells. For example, the following tumor cell lines may be used: UACC257 (high antigen density of the antigen PRAME (preferentially expressed antigen in melanoma)), A375 (low antigen density of the antigen PRAME), or MCF7 (negative for the antigen PRAME). Cells are cocultured for up to 21 days in an IncuCyte and are imaged about every 2 hours. Effector (T cell product) to target (tumor cell line) ratio (E/T) is as follows: about 4:1 E/T for UACC257 (about 40,000 effectors to about 10,000 tumor cells), about 8:1 E/T for A375 (about 80,000 effectors to about 10,000 tumor cells), or about 4:1 E/T for MCF7 (about 40,000 effectors to about 10,000 tumor cells). Effector numbers are normalized to TCR positivity to account for the variability in transduction efficiency between cellular products. Prior to co-culture setup, the tumor cells are seeded onto 96-well IncuCyte ImageLock plates and allowed to attach for about 1-4 hours before effector cells are added. Tumor cell-only wells are included as controls for each serial killing IncuCyte assay performed. Effectors and tumor cells are allowed to coculture for 3-4 days before an add-back is performed in which about 10,000 fresh tumor cells are added to the wells (referred to as a tumor challenge or stimulation). The number of tumor challenges may vary between experiments but typically, 3-6 tumor challenges are performed. 16-24 hours after coculture is initiated and after every subsequent add-back, about 50-100 μ l of supernatant from the wells is harvested for use in IFN γ ELISA or Luminex assays. Data acquisition and processing is performed by the Incucyte® S3 Live-Cell Analysis Instrument with values graphed using Prism/GraphPad statistical software.

EXAMPLE 19**T Cell Phenotype**

[00689] Prior to the coculture setup (time 0) for the serial killing IncuCyte assays, a fraction (about $1-2 \times 10^6$ cells per condition) of cellular products are stained for surfaces markers indicative of T cell activation and exhaustion and assessed for expression by flow cytometry. The panel includes a live-dead stain and assesses the expression of 12 different surfaces molecules: CD8, CD3, CD4, engineered TCR, TIM-3, TIGIT, 4-1BB, 2B4, CD39, PD-1, CD69, and LAG3. Upon the completion of the serial killing IncuCyte assay, cells are harvested and stained with the same panel, allowing for the comparison of ICI marker expression pre- and post-antigen exposure. Data analysis is performed using FlowJo and graphed using Prism/GraphPad statistical software.

EXAMPLE 20**IFN γ Secretion Assay**

[00690] 16-24 hours after coculture is initiated for the serial killing IncuCyte assay and after every subsequent add-back of tumor cells, about 50-100 μ l of supernatant from the wells is harvested for use in cytokine detection assays. Supernatants are stored at about -80°C until use. For interferon γ (IFN γ) ELISAs, supernatants are thawed and diluted with assay buffer. The dilutions are dependent on the tumor cell line used for the coculture and the time point the supernatant was collected. Typically, the following dilutions are used: Against UACC257, 1:20 for post-stimulation #1-3 and 1:10 for post- stimulation #4-6; against A375, 1:5 for post-stimulation #1-3 and 1:2 for post- stimulation #4-6; against MCF7, 1:5 for post- stimulation #1-3. IFN γ ELISAs are conducted with the human IFN γ Quantikine ELISA kit from R&D Systems following the manufacturer's protocol with plates are read at 450nm wavelength using the Synergy 2 microplate reader. Data analysis is performed using Prism/GraphPad statistical software.

EXAMPLE 21**T cell manufacturing**

[00691] TCR-transduced products co-expressing TCR specific for PRAME-004 and mbIL15 were generated using a standard manufacturing process. Briefly, donor peripheral blood mononuclear cells (PBMCs) were isolated from healthy donor leukaphereses and cryopreserved. PBMCs are later thawed in TexMACS medium supplemented with 5% by volume human AB serum ("Complete TexMACS"), washed, resuspended in Complete TexMACS, and treated with benzonase nuclease for a short duration. Cells are then rested in a cell stack. Following rest, PBMC are counted, concentration-adjusted, and added to tissue culture bags coated with

immobilized anti-CD3 and anti-CD28 antibodies for activation. Cells are activated overnight at 37°C.

[00692] Following activation, cells are removed from the activation bags, washed, and counted. They are then added to G-Rex vessels containing a transduction master mix. For transduced cells, lentiviral supernatant was added at 2.5 µL per million activated PBMC. For non-transduced (NT) cells, no lentivirus was added.

[00693] The next day (~24 hr) following transduction, Complete TexMACS medium containing IL-7 (10ng/ml) and IL-15 (50 ng/mL) were added to the vessel maximum volume and allowed to expand. On day 7, cells are harvested, washed, concentrated, and cryopreserved in CryoStor CS5.

D-1: Coat bags

D+0: Thaw, rest, & activation

D+1: Transduction

D+2: Media/cytokine addition (feed)

D+7: Harvest & cryopreserve

[00694] Flow cytometry was used to get transgene frequencies with analysis performed using FlowJo software. Harvest metrics including TCR frequency, mbIL15+TCR+ DP frequency, fold expansion, and total TCR+ cells are shown in FIG. 71A-D. All constructs were expressed.

EXAMPLE 22

Cytotoxicity Assay & IFN γ secretion

[00695] T cell products were previously generated using the manufacturing described in Example 21 were thawed, washed, and resuspended in Complete TexMACS and treated with benzonase nuclease (25 U/mL) for 15 minutes. Cells are then rested overnight in Complete TexMACS within a Grex vessel at 37°C (no exogenous cytokines are added for overnight rest).

[00696] The next day, tumor lines are harvested using 0.05% trypsin, washed, and counted. Red fluorescent protein (RFP)-labeled tumor cells were plated at 10,000 per well in a flat-bottomed 96-well ImageLock plate in 100 µL of Complete TexMACS. Plates were placed in an incubator at 37°C until effector T cells were ready for plating.

[00697] Overnight-rested effector T cells were removed from the incubator and counted. Depending on the intended effector-to-target (E:T) ratio, a certain number of effectors cells were added in 100 µL to their respective well on the 96-well plate. Effector numbers were normalized with respect to T cell receptor (TCR)-positive cells with the total number of T cells added adjusted to account for the transduction efficiency. Typical E:T ratios include, but are not limited

to, 10:1, 8:1, 5:1, 4:1, 3:1, or 1:1 depending on the target cells used and the question(s) being investigated.

[00698] Effector/target co-culture plates were placed into the IncuCyte S3 imager at 37°C and 5% CO₂ and imaged every 4 hours for the duration of the assay (typically ~3 to 12 days).

[00699] Supernatant, if needed for cytokine analysis, was collected between 16 and 24 hours after the initiation of co-culture, and the plate replenished with fresh Complete TexMACS. Harvested supernatant was frozen down at -80°C for use in downstream IFN γ ELISAs.

[00700] In assays including multiple tumor challenges, co-culture plates were removed 3-4 days following the last tumor cell stimulation and 50 μ L of supernatant was removed using a micropipette. Complete TexMACS medium containing the same number of tumor target cells as at assay initiation was added to bring each well to full volume. If a given condition did not require the addition of tumor cells, they were provided with fresh medium. Cells were placed back in the IncuCyte until the next tumor cell stimulation timepoint.

[00701] Data was exported from the IncuCyte S3 software into Microsoft Excel and GraphPad Prism for further analysis. Fold tumor growth (RFP+ cell count) was normalized to 0 hr timepoint.

[00702] Results are shown in FIGs. 72-75. All products were expressed with the majority of mbIL15-containing products showing increased killing and cytokine production upon repeated antigen stimulation compared to TCR only ("TCR").

EXAMPLE 23

Cell phenotyping

[00703] Flow cytometry was performed on overnight-rested T cell products produced as described in Example 21 before or after antigen stimulation (through co-culture with tumor cells). For the "post-antigen" stimulation analysis, co-culture wells from the IncuCyte cytotoxicity assay described in Example 22 were harvested and used after the IncuCyte assay concluded. Product was stained with antibodies against memory and exhaustion markers. Flow analysis was performed using FlowJo software.

[00704] Results are shown in FIG. 76-77. Constructs show comparable memory subset distribution pre-antigen exposure with a predominant shift to Tem after antigen exposure. Exhaustion marker frequencies are similar across all constructs prior to antigen exposure.

EXAMPLE 24

Cell Death & Apoptosis Assay

[00705] Overnight-rested effector T cell product was co-cultured with antigen (PRAME)-positive tumor cells lines as described in the IncuCyte assay method of Example 22 except in a 24-well rather than a 96-well tissue culture plate. After co-culture setup, plates were incubated at 37°C and 5% CO₂ with re-stimulations occurring every 2-3 days. A total of four stimulations were performed. Wells were harvested after ~9-10 days in culture and the cell mixture analyzed by flow cytometry for dead and apoptotic cells. Flow analysis was performed using FlowJo software.

[00706] Results are shown in FIG. 78. All mbIL15-containing constructs exhibited improved survival compared to TCR only ("TCR") or non-transduced (NT") products.

EXAMPLE 25

Proliferation

[00707] T cell product was thawed and rested as in the IncuCyte cytotoxicity assay described in Example 22. Tumor cells were similarly plated as in the IncuCyte cytotoxicity assay but in 1 mL per well in a 24-well rather than a 96-well tissue culture plate.

[00708] On the day of co-culture, effector T cells were counted, washed, and resuspended in PBS containing a CellTrace Violet proliferation dye at 1:1000 dilution (1 µL dye per mL PBS) and incubated for 20 minutes at 37°C.

[00709] After labeling incubation, Complete TexMACS with 5% human AB serum was added in excess to bind remaining free dye and incubated for another 5 minutes at 37°C.

[00710] Labeled effector T cells were then washed, counted, and resuspended in Complete TexMACS and added in 1 mL per well to previously prepared tumor targets for a total of 2 mL per well. E:T ratios varied but mirrored the IncuCyte cytotoxicity assays as described in Example 22 to ensure comparability.

Co-cultured tumor target and effector T cells were incubated for ~6 days at 37°C after which point they were harvested, washed, and stained with a panel consisting of a TCR-specific tetramer and antibodies against surface antigens.

[00711] Proliferation modeling and statistics were generated using the Proliferation Modeling feature of FlowJo.

[00712] Results are shown in FIG. 79.

EXAMPLE 26

Persistence Assay

[00713] Overnight-rested effector T cell product was cultured in a Grex 24-well vessel at a concentration of 1.0e6 cells/ml either in the absence of any exogenous IL-7 & IL-15 addition or

in the presence of IL-7 & IL-15 for up to 31 days. Every 3-4 days cells were counted using a cellometer and a 50% fresh medium change was performed. Complete TexMACS was used for the entire duration of the assay. After 31 days, cells were counted and then used in a IncuCyte cytotoxicity assay against antigen-positive tumor cell lines through one stimulation.

[00714] IncuCyte data was exported from the IncuCyte S3 software into Microsoft Excel and GraphPad Prism for further analysis. Fold tumor growth (RFP+ cell count) was normalized to 0 hr timepoint.

[00715] Results are shown in FIGs. 80 and 81. All mbIL15-containing products persisted through 31 days in culture in the absence of cytokine addition and no antigen stimulation. Cytolytic activity was retained in all products containing mbIL15 against antigen positive tumor cell lines.

The present invention may be defined by the following aspects:

1. A nucleic acid encoding a fusion polypeptide of Formula I:

N-terminus-P6-PL-P7-C-terminus [I]

wherein P6 and P7 are each independently first and second polypeptides and PL is a linker, wherein PL comprises SEQ ID NO: 387 or 389 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 387 or 389.

2. A nucleic acid comprising formula II:

5'-N6-NL-N7-3' [II]

wherein N6 and N7 each independently encode first and second polypeptides and NL encodes a linker, wherein NL comprises SEQ ID NO: 388 or 390 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 388 or 390.

3. A nucleic acid encoding a polypeptide comprising SEQ ID NO: 311, 313, or 315 or a polypeptide at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 311, 313, or 315.

4. A nucleic acid comprising SEQ ID NO: 312, 314, or 316 or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 312, 314, or 316.

5. A nucleic acid encoding (i) a polypeptide comprising SEQ ID NO: 307 fused directly or indirectly to an N terminus of a polypeptide comprising any of SEQ ID NO: 311, 313, or 315 or (ii) a polypeptide at least about 95%, at least about 96%, at least about 97%, at least about

98%, at least about 99%, or about 100% identical to SEQ ID NO: 307 fused directly or indirectly to a polypeptide at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to any of SEQ ID NO: 311, 313, or 315.

6. The nucleic acid of aspect 5, further comprising a nucleic acid encoding a signal peptide directly or indirectly fused to an N terminus of SEQ ID NO: 307 or to an N terminus of a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 307.

7. The nucleic acid of aspect 6, wherein the signal peptide is derived from an IgE polypeptide.

8. The nucleic acid of aspect 7, wherein the signal peptide derived from an IgE polypeptide comprises SEQ ID NO: 367 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

9. A nucleic acid comprising (i) SEQ ID NO: 308 fused directly or indirectly to a 5' end of any of SEQ ID NO: 312, 314, or 316 or (ii) a sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 308 fused directly or indirectly to the 5' end of any of a sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to any of SEQ ID NO: 312, 314, or 316.

10. The nucleic acid of aspect 9, further comprising a nucleic acid encoding a signal peptide directly or indirectly fused to the 5' end of SEQ ID NO: 308 or to 5' end of a sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 308.

11. The nucleic acid of aspect 10, wherein the signal peptide is derived from an IgE polypeptide.

12. The nucleic acid of aspect 11, wherein the signal peptide derived from an IgE polypeptide comprises SEQ ID NO: 368 or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

13. A nucleic acid encoding a polypeptide comprising SEQ ID NO: 317, 321, 325, 327, 329, 331, or 333 or a polypeptide at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 317, 321, 325, 327, 329, 331, or 333.

- 14.** The nucleic acid of aspect 13, further comprising a nucleic acid encoding a signal peptide directly or indirectly fused to an N terminus of SEQ ID NO: 317, 321, 325, 327, 329, 331, or 333 or to an N terminus of a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 317, 321, 325, 327, 329, 331, or 333.
- 15.** The nucleic acid of aspect 14, wherein the signal peptide is derived from an IgE polypeptide.
- 16.** The nucleic acid of aspect 15, wherein the signal peptide derived from an IgE polypeptide comprises SEQ ID NO: 367 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.
- 17.** A nucleic acid comprising SEQ ID NO: 318, 322, 326, 328, 330, 332, or 334 or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 318, 322, 326, 328, 330, 332, or 334.
- 18.** The nucleic acid of aspect 17, further comprising a nucleic acid encoding a signal peptide directly or indirectly fused to the 5' end of SEQ ID NO: 318, 322, 326, 328, 330, 332, or 334 or to 5' end of a sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 318, 322, 326, 328, 330, 332, or 334.
- 19.** The nucleic acid of aspect 18, wherein the signal peptide is derived from an IgE polypeptide.
- 20.** The nucleic acid of aspect 19, wherein the signal peptide derived from an IgE polypeptide comprises SEQ ID NO: 368 or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.
- 21.** A nucleic acid encoding a polypeptide comprising SEQ ID NO: 337, 341, 345, 347, 349, 351, or 353 or a polypeptide at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 337, 341, 345, 347, 349, 351, or 353.
- 22.** A nucleic acid comprising SEQ ID NO: 338, 342, 346, 348, 350, 352, or 354 or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 338, 342, 346, 348, 350, 352, or 354.
- 23.** A vector comprising the nucleic acid of any one of aspects 1-22.

- 24.** The vector of aspect 23, wherein the vector further comprises a post-transcriptional regulatory element (PRE) sequence selected from Woodchuck PRE (WPRE) (SEQ ID NO: 264), Woodchuck PRE (WPRE) mutant 1 (SEQ ID NO: 256), Woodchuck PRE (WPRE) mutant 2 (SEQ ID NO: 257), and hepatitis B virus (HBV) PRE (HPRE) (SEQ ID NO: 437).
- 25.** The vector of aspect 24, wherein the post-transcriptional regulatory element (PRE) sequence is the Woodchuck PRE (WPRE) mutant 1 comprising the nucleic acid sequence of SEQ ID NO: 256.
- 26.** The vector of aspect 24, wherein the post-transcriptional regulatory element (PRE) sequence is the Woodchuck PRE (WPRE) mutant 2 comprising the nucleic acid sequence of SEQ ID NO: 257.
- 27.** The vector of any one of aspects 23-26, wherein the vector further comprises a promoter selected from cytomegalovirus (CMV) promoter, phosphoglycerate kinase (PGK) promoter, myelin basic protein (MBP) promoter, glial fibrillary acidic protein (GFAP) promoter, modified MoMuLV LTR comprising myeloproliferative sarcoma virus enhancer (MNDU3), Ubiquitin C promoter, EF-1 alpha promoter, or Murine Stem Cell Virus (MSCV) promoter.
- 28.** The vector of aspect 27, wherein the promoter is a Murine Stem Cell Virus (MSCV) promoter.
- 29.** The vector of any one of aspects 23-28, wherein the vector is a viral vector or a non-viral vector.
- 30.** The vector of aspect 29, wherein the vector is a viral vector.
- 31.** The vector of aspect 29 or aspect 30, wherein the viral vector is selected from adenoviruses, poxviruses, alphaviruses, arenaviruses, flaviruses, rhabdoviruses, retroviruses, lentiviruses, herpesviruses, paramyxoviruses, picornaviruses, and combinations thereof.
- 32.** The vector of any one of aspects 29-31, wherein the viral vector is pseudotyped with an envelope protein of a virus selected from a native feline endogenous virus (RD114), a version of RD114 (RD114TR), gibbon ape leukemia virus (GALV), a version of GALV (GALV-TR), amphotropic murine leukemia virus (MLV 4070A), baculovirus (GP64), vesicular stomatitis virus (VSV-G), fowl plague virus (FPV), Ebola virus (EboV), baboon retroviral envelope glycoprotein (BaEV), and lymphocytic choriomeningitis virus (LCMV).
- 33.** The vector of any one of aspects 23-32, wherein the vector is a lentiviral vector.
- 34.** The vector of any one of aspects 23-33, wherein the vector further comprises a nucleic acid encoding a chimeric antigen receptor (CAR).
- 35.** A T cell or natural killer (NK) cell (i) transduced with the nucleic acid of any one of aspects 1-22 or (ii) comprising the vector of any one of aspects 23-34.

- 36.** The T cell or natural killer (NK) cell of aspect 35, wherein the cell is an $\alpha\beta$ T cell, a $\gamma\delta$ T cell, a natural killer T cell, a natural killer (NK) cell, or any combination thereof.
- 37.** The T cell or natural killer (NK) cell of aspect 36, wherein the $\alpha\beta$ T cell is a CD4⁺ T cell.
- 38.** The T cell or natural killer (NK) cell of aspect 36, wherein the $\alpha\beta$ T cell is a CD8⁺ T cell.
- 39.** The T cell or natural killer (NK) cell of aspect 36, wherein the $\gamma\delta$ T cell is a V γ 9V δ 2⁺ T cell.
- 40.** The nucleic acid of any one of aspects 5-22 further comprising a nucleic acid encoding (a) at least one TCR polypeptide comprising an α chain and a β chain, (b) at least one CD8 polypeptide comprising (i) an α chain, (ii) a β chain, or (iii) both an α chain and a β chain, or (c) at least one TCR polypeptide comprising an α chain and a β chain and at least one CD8 polypeptide comprising (i) an α chain, (ii) a β chain, or (iii) both an α chain and a β chain.
- 41.** A polypeptide, polypeptides, or fusion polypeptide encoded by the nucleic acid of any one of aspects 1-22 or 40.
- 42.** A polypeptide or fusion polypeptide comprising an amino acid sequence at least about 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 311, 313, 315, 317, 319, 321, 323, 325, 327, 329, 331, 333, 337, 339, 341, 343, 345, 347, 349, 351, or 353.
- 43.** A fusion polypeptide comprising a polypeptide at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 307 fused directly or indirectly to an N terminus of any of a polypeptide at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to any of SEQ ID NO: 311, 313, or 315.
- 44.** The fusion polypeptide of aspect 43, further comprising a signal peptide directly or indirectly fused to an N terminus of a polypeptide at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 307.
- 45.** The fusion polypeptide of aspect 44, wherein the signal peptide is derived from an IgE polypeptide.
- 46.** The fusion polypeptide of aspect 45, wherein the signal peptide derived from an IgE polypeptide comprises SEQ ID NO: 367 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.
- 47.** A vector comprising the nucleic acid of aspect 40.

- 48.** The vector of aspect 47, wherein the vector further comprises a nucleic acid encoding a 2A peptide or an internal ribosome entry site (IRES) positioned between the nucleic acid encoding the CD8 α chain and the nucleic acid encoding the CD8 β chain.
- 49.** The vector of aspect 47 or 48, wherein the vector further comprises a nucleic acid encoding a 2A peptide or an IRES positioned between the nucleic acid encoding the TCR α chain and the nucleic acid encoding the TCR β chain.
- 50.** The vector of aspect 49, wherein the 2A peptide is P2A (SEQ ID NO: 93), T2A (SEQ ID NO: 94), E2A (SEQ ID NO: 95), or F2A (SEQ ID NO: 96).
- 51.** The vector of aspect 49 or 50, wherein the IRES is selected from the group consisting of IRES from picornavirus, IRES from flavivirus, IRES from pestivirus, IRES from retrovirus, IRES from lentivirus, IRES from insect RNA virus, and IRES from cellular mRNA.
- 52.** The vector of any one of aspects 47-51, wherein the vector further comprises a post-transcriptional regulatory element (PRE) sequence selected from a Woodchuck PRE (WPRE) (SEQ ID NO: 264), Woodchuck PRE (WPRE) mutant 1 (SEQ ID NO: 256), Woodchuck PRE (WPRE) mutant 2 (SEQ ID NO: 257), or hepatitis B virus (HBV) PRE (HPRE) (SEQ ID NO: 437).
- 53.** The vector of aspect 52, wherein the post-transcriptional regulatory element (PRE) sequence is a Woodchuck PRE (WPRE) mutant 1 comprising the nucleic acid sequence of SEQ ID NO: 256.
- 54.** The vector of aspect 52, wherein the post-transcriptional regulatory element (PRE) sequence is a Woodchuck PRE (WPRE) mutant 2 comprising the nucleic acid sequence of SEQ ID NO: 257.
- 55.** The vector of any one of aspects 47-54, wherein the vector further comprises a promoter selected from cytomegalovirus (CMV) promoter, phosphoglycerate kinase (PGK) promoter, myelin basic protein (MBP) promoter, glial fibrillary acidic protein (GFAP) promoter, modified MoMuLV LTR comprising myeloproliferative sarcoma virus enhancer (MNDU3), Ubiquitin C promoter, EF-1 alpha promoter, or Murine Stem Cell Virus (MSCV) promoter.
- 56.** The vector of aspect 55, wherein the promoter is a Murine Stem Cell Virus (MSCV) promoter.
- 57.** The vector of any one of aspects 47-56, wherein the vector is a viral vector or a non-viral vector.
- 58.** The vector of aspect 57, wherein the vector is a viral vector.

- 59.** The vector of aspect 58, wherein the viral vector is selected from adenoviruses, poxviruses, alphaviruses, arenaviruses, flaviviruses, rhabdoviruses, retroviruses, lentiviruses, herpesviruses, paramyxoviruses, picornaviruses, and any combination thereof.
- 60.** The vector of aspect 58 or 59, wherein the viral vector is pseudotyped with an envelope protein of a virus selected from the native feline endogenous virus (RD114), a version of RD114 (RD114TR), gibbon ape leukemia virus (GALV), a version of GALV (GALV-TR), amphotropic murine leukemia virus (MLV 4070A), baculovirus (GP64), vesicular stomatitis virus (VSV-G), fowl plague virus (FPV), Ebola virus (EboV), or baboon retroviral envelope glycoprotein (BaEV), and lymphocytic choriomeningitis virus (LCMV).
- 61.** The vector of any one of aspects 47-60, wherein the vector is a lentiviral vector.
- 62.** The vector of any one of aspects 47-61, wherein the vector further comprises a nucleic acid encoding a chimeric antigen receptor (CAR).
- 63.** A T cell and/or natural killer cell comprising the vector of any one of aspects 47-62.
- 64.** The T cell and/or natural killer cell of aspect 63, wherein the T cell is an $\alpha\beta$ T cell, a $\gamma\delta$ T cell, a natural killer T cell, or any combination thereof.
- 65.** The T cell and/or natural killer cell of aspect 64, wherein the $\alpha\beta$ T cell is a CD4⁺ T cell.
- 66.** The T cell and/or natural killer cell of aspect 64, wherein the $\alpha\beta$ T cell is a CD8⁺ T cell.
- 67.** The T cell and/or natural killer cell of aspect 64, wherein the $\gamma\delta$ T cell is a V γ 9V δ 2⁺ T cell.
- 68.** A composition comprising the T cell and/or natural killer cell of any one of aspects 63-67.
- 69.** The composition of aspect 68, wherein the composition is a pharmaceutical composition.
- 70.** The composition of aspect 68 or aspect 69, wherein the composition further comprises an adjuvant, excipient, carrier, diluent, buffer, stabilizer, or a combination thereof.
- 71.** The composition of aspect 70, wherein the adjuvant is an anti-CD40 antibody, imiquimod, resiquimod, GM-CSF, cyclophosphamide, sunitinib, bevacizumab, atezolizumab, interferon-alpha, interferon-beta, CpG oligonucleotides and derivatives, poly(I:C) and derivatives, RNA, sildenafil, particulate formulations with poly(lactide co-glycolide) (PLG), virosomes, interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-4 (IL-4), interleukin-7 (IL-7), interleukin-12 (IL-12), interleukin-13 (IL-13), interleukin-15 (IL-15), interleukin-21 (IL-21), interleukin-23 (IL-23), or any combination thereof.

- 72.** The composition of aspect 70 or aspect 71, wherein the adjuvant is IL-2, IL-7, IL-12, IL-15, IL-21, or any combination thereof.
- 73.** A method of preparing T cells and/or natural killer cells for immunotherapy comprising:
- isolating T cells and/or natural killer cells from a blood sample of a human subject,
 - activating the isolated T cells and/or natural killer cells,
 - transducing the activated T cells and/or natural killer cells with the nucleic acid of aspect 40 or the vector of any one of aspects 47-62, and
 - expanding the transduced T cells and/or natural killer cells.
- 74.** The method of aspect 73, further comprising isolating CD4+CD8+ T cells from the transduced T cells and/or natural killer cells and expanding the isolated CD4+CD8+ transduced T cells.
- 75.** The method of aspect 73 or aspect 74, wherein the blood sample comprises peripheral blood mononuclear cells (PMBC).
- 76.** The method of any one of aspects 73-75, wherein the activating comprises contacting the T cells and/or natural killer cells with an anti-CD3 and an anti-CD28 antibody.
- 77.** The method of any one of aspects 73-76, wherein the T cell is a CD4+ T cell.
- 78.** The method of any one of aspects 73-76, wherein the T cell is a CD8+ T cell.
- 79.** The method of aspect 73-78, wherein the T cell is a $\gamma\delta$ T cell or an $\alpha\beta$ T cell.
- 80.** The method of any one of aspects 73-79, wherein the activation, the expanding, or both are in the presence of a combination of IL-2 and IL-15 and optionally with zoledronate.
- 81.** A method of treating a patient who has cancer, comprising administering to the patient the composition of any one of aspects 98-72, wherein the cancer is selected from the group consisting of non-small cell lung cancer, small cell lung cancer, melanoma, liver cancer, breast cancer, uterine cancer, Merkel cell carcinoma, pancreatic cancer, gallbladder cancer, bile duct cancer, colorectal cancer, urinary bladder cancer, kidney cancer, leukemia, ovarian cancer, esophageal cancer, brain cancer, gastric cancer, and prostate cancer.
- 82.** A method of eliciting an immune response in a patient who has cancer, comprising administering to the patient the composition of any one of aspects 78-72, wherein the cancer is selected from the group consisting of non-small cell lung cancer, small cell lung cancer, melanoma, liver cancer, breast cancer, uterine cancer, Merkel cell carcinoma, pancreatic cancer, gallbladder cancer, bile duct cancer, colorectal cancer, urinary bladder cancer, kidney cancer, leukemia, ovarian cancer, esophageal cancer, brain cancer, gastric cancer, and prostate cancer.

83. The method of aspect 81 or 82, wherein the T cell and/or natural killer cell kills cancer cells that present a peptide in a complex with an MHC molecule on a cell surface.

84. A nucleic acid comprising:

(a) a nucleic acid encoding (i) a T-cell receptor (TCR) comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain and a β chain, or (ii) a TCR comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain without a β chain, and

(b) a nucleic acid encoding an IL-15/IL-15R α fusion polypeptide,

wherein the TCR α chain and the TCR β chain are selected from SEQ ID NO: 15 and 16, 17 and 18, 19 and 20, 21 and 22, 23 and 24, 25 and 26, 27 and 28, 29 and 30, 31 and 32, 33 and 34, 35 and 36, 37 and 38, 39 and 40, 41 and 42, 43 and 44, 45 and 46, 47 and 48, 49 and 50, 51 and 52, 53 and 54, 55 and 56, 57 and 58, 59 and 60, 61 and 62, 63 and 64, 65 and 66, 67 and 68, 69 and 70, 71 and 303, 304 and 74, 75 and 76, 77 and 78, 79 and 80, 81 and 82, 83 and 84, 85 and 86, 87 and 88, 89 and 90, and 91 and 92;

wherein the CD8 α chain is SEQ ID NO: 7, 258, 259, 262, or a variant thereof;

wherein, if present, the CD8 β chain is SEQ ID NO: 8, 9, 10, 11, 12, 13, or 14;

and

wherein the IL-15/IL-15R α fusion polypeptide is selected from (i) SEQ ID NO: 307 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto, directly or indirectly fused to an N terminus of SEQ ID NO: 311 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto, with or without a linker therebetween; (ii) SEQ ID NO: 307 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto, directly or indirectly fused to an N terminus of SEQ ID NO: 313 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto, with or without a linker therebetween; or (iii) SEQ ID NO: 307 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto, directly or indirectly fused to an N terminus of SEQ ID NO: 315 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto, with or without a linker therebetween.

- 85.** The nucleic acid of aspect 84, wherein the IL-15/IL-15R α fusion polypeptide further comprises a signal peptide directly or indirectly fused to the N terminus of SEQ ID NO: 307 of any of (i), (ii), or (iii) or to the N terminus of a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 307 of any of (i), (ii), or (iii).
- 86.** The nucleic acid of aspect 85, wherein the signal peptide is derived from an IgE polypeptide.
- 87.** The nucleic acid of aspect 86, wherein the signal peptide derived from an IgE polypeptide comprises SEQ ID NO: 367 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.
- 88.** A nucleic acid comprising:
- (a) a nucleic acid encoding (i) a T-cell receptor (TCR) comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain and a β chain, or (ii) a TCR comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain without a β chain, and
 - (b) a nucleic acid encoding an IL-15/IL-15R α fusion polypeptide,
wherein the TCR α chain and the TCR β chain are selected from SEQ ID NO: 15 and 16, 17 and 18, 19 and 20, 21 and 22, 23 and 24, 25 and 26, 27 and 28, 29 and 30, 31 and 32, 33 and 34, 35 and 36, 37 and 38, 39 and 40, 41 and 42, 43 and 44, 45 and 46, 47 and 48, 49 and 50, 51 and 52, 53 and 54, 55 and 56, 57 and 58, 59 and 60, 61 and 62, 63 and 64, 65 and 66, 67 and 68, 69 and 70, 71 and 303, 304 and 74, 75 and 76, 77 and 78, 79 and 80, 81 and 82, 83 and 84, 85 and 86, 87 and 88, 89 and 90, and 91 and 92;
wherein the CD8 α chain is SEQ ID NO: 7, 258, 259, 262, or a variant thereof;
wherein, if present, the CD8 β chain is SEQ ID NO: 8, 9, 10, 11, 12, 13, or 14;
and
wherein the IL-15/IL-15R α fusion polypeptide is selected from SEQ ID NO: 317, 319, 321, 323, 325, 327, 329, 331, or 333, or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 317, 319, 321, 323, 325, 327, 329, 331, or 333.
- 89.** The nucleic acid of aspect 88, wherein the IL-15/IL-15R α fusion polypeptide further comprises a signal peptide directly or indirectly fused to an N terminus of SEQ ID NO: SEQ ID NO: 317, 319, 321, 323, 325, 327, 329, 331, or 333, or directly or indirectly fused to an N terminus of a sequence at least about 95%, at least about 96%, at least about 97%, at least about

98%, at least about 99%, or about 100% identical to SEQ ID NO: 317, 319, 321, 323, 325, 327, 329, 331, or 333.

90. The nucleic acid of aspect 89, wherein the signal peptide is derived from an IgE polypeptide.

91. The nucleic acid of aspect 90, wherein the signal peptide derived from an IgE polypeptide comprises SEQ ID NO: 367 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

92. A nucleic acid comprising:

(a) a nucleic acid encoding (i) a T-cell receptor (TCR) comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain and a β chain, or (ii) a TCR comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain without a β chain, and

(b) a nucleic acid encoding a fusion polypeptide comprising (i) SEQ ID NO: 367 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 367 fused to (ii) an N terminus of an IL-15/IL-15R α fusion polypeptide,

wherein the TCR α chain and the TCR β chain are selected from SEQ ID NO: 15 and 16, 17 and 18, 19 and 20, 21 and 22, 23 and 24, 25 and 26, 27 and 28, 29 and 30, 31 and 32, 33 and 34, 35 and 36, 37 and 38, 39 and 40, 41 and 42, 43 and 44, 45 and 46, 47 and 48, 49 and 50, 51 and 52, 53 and 54, 55 and 56, 57 and 58, 59 and 60, 61 and 62, 63 and 64, 65 and 66, 67 and 68, 69 and 70, 71 and 303, 304 and 74, 75 and 76, 77 and 78, 79 and 80, 81 and 82, 83 and 84, 85 and 86, 87 and 88, 89 and 90, and 91 and 92;

wherein the CD8 α chain is SEQ ID NO: 7, 258, 259, 262, or a variant thereof;

wherein, if present, the CD8 β chain is SEQ ID NO: 8, 9, 10, 11, 12, 13, or 14;

and

wherein the nucleic acid of (b) encodes a fusion polypeptide selected from SEQ ID NO: 337, 339, 341, 343, 345, 347, 349, 351, or 353, or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 337, 339, 341, 343, 345, 347, 349, 351, or 353.

93. A nucleic acid comprising:

(a) a nucleic acid encoding (i) a T-cell receptor (TCR) comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain and a β chain, or (ii) a TCR comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain without a β chain, and

(b) a nucleic acid encoding an IL-15/IL-15R α fusion polypeptide,

wherein the TCR α chain and the TCR β chain are selected from SEQ ID NO: 15 and 16, 17 and 18, 19 and 20, 21 and 22, 23 and 24, 25 and 26, 27 and 28, 29 and 30, 31 and 32, 33 and 34, 35 and 36, 37 and 38, 39 and 40, 41 and 42, 43 and 44, 45 and 46, 47 and 48, 49 and 50, 51 and 52, 53 and 54, 55 and 56, 57 and 58, 59 and 60, 61 and 62, 63 and 64, 65 and 66, 67 and 68, 69 and 70, 71 and 303, 304 and 74, 75 and 76, 77 and 78, 79 and 80, 81 and 82, 83 and 84, 85 and 86, 87 and 88, 89 and 90, and 91 and 92;

wherein the CD8 α chain is SEQ ID NO: 7, 258, 259, 262, or a variant thereof;

wherein, if present, the CD8 β chain is SEQ ID NO: 8, 9, 10, 11, 12, 13, or 14;

and

wherein the IL-15/IL-15R α fusion polypeptide is selected from SEQ ID NO: 317, 321, 325, 327, 329, 331, or 333 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 317, 321, 325, 327, 329, 331, or 333.

94. The nucleic acid of aspect 93, wherein the IL-15/IL-15R α fusion polypeptide further comprises a signal peptide directly or indirectly fused to an N terminus of SEQ ID NO: 317, 321, 325, 327, 329, 331, or 333, or to an N terminus of a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 317, 321, 325, 327, 329, 331, or 333.

95. The nucleic acid of aspect 94, wherein the signal peptide is derived from an IgE polypeptide.

96. The nucleic acid of aspect 95, wherein the signal peptide derived from an IgE polypeptide comprises SEQ ID NO: 367 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

97. A nucleic acid comprising:

(a) a nucleic acid encoding (i) a T-cell receptor (TCR) comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain and a β chain, or (ii) a TCR comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain without a β chain, and

(b) a nucleic acid encoding a fusion polypeptide comprising (i) SEQ ID NO: 367 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 367 fused to (ii) an N terminus of an IL-15/IL-15R α fusion polypeptide,

wherein the TCR α chain and the TCR β chain are selected from SEQ ID NO: 15 and 16, 17 and 18, 19 and 20, 21 and 22, 23 and 24, 25 and 26, 27 and 28, 29 and 30, 31 and 32, 33 and 34, 35 and 36, 37 and 38, 39 and 40, 41 and 42, 43 and 44, 45 and 46, 47 and 48, 49 and 50, 51 and 52, 53 and 54, 55 and 56, 57 and 58, 59 and 60, 61 and 62, 63 and 64, 65 and 66, 67 and 68, 69 and 70, 71 and 303, 304 and 74, 75 and 76, 77 and 78, 79 and 80, 81 and 82, 83 and 84, 85 and 86, 87 and 88, 89 and 90, and 91 and 92;

wherein the CD8 α chain is SEQ ID NO: 7, 258, 259, 262, or a variant thereof;

wherein, if present, the CD8 β chain is SEQ ID NO: 8, 9, 10, 11, 12, 13, or 14;

and

wherein the nucleic acid of (b) encodes a fusion polypeptide selected from SEQ ID NO: 337, 341, 345, 347, 349, 351, or 353 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 337, 341, 345, 347, 349, 351, or 353.

98. A nucleic acid comprising:

(a) a nucleic acid encoding (i) a T-cell receptor (TCR) comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain and a β chain, or (ii) a TCR comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain without a β chain, and

(b) a nucleic acid encoding an IL-15/IL-15R α fusion polypeptide,

wherein the TCR α chain and the TCR β chain are selected from SEQ ID NO: 15 and 16, 57 and 58, 59 and 60, 61 and 62, 63 and 64, 65 and 66, 67 and 68, 69 and 70, and 71 and 303;

wherein the CD8 α chain is SEQ ID NO: 7, 258, 259, 262, or a variant thereof;

and

wherein, if present, the CD8 β chain is SEQ ID NO: 8, 9, 10, 11, 12, 13, or 14.

99. The nucleic acid of aspect 98, wherein the IL-15/IL-15R α fusion polypeptide comprises SEQ ID NO: 317 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

100. The nucleic acid of aspect 98, wherein the IL-15/IL-15R α fusion polypeptide comprises SEQ ID NO: 319 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

101. The nucleic acid of aspect 98, wherein the IL-15/IL-15R α fusion polypeptide comprises SEQ ID NO: 321 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

- 102.** The nucleic acid of aspect 98, wherein the IL-15/IL-15R α fusion polypeptide comprises SEQ ID NO: 323 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.
- 103.** The nucleic acid of aspect 98, wherein the IL-15/IL-15R α fusion polypeptide comprises SEQ ID NO: 325 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.
- 104.** The nucleic acid of aspect 98, wherein the IL-15/IL-15R α fusion polypeptide comprises SEQ ID NO: 327 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.
- 105.** The nucleic acid of aspect 98, wherein the IL-15/IL-15R α fusion polypeptide comprises SEQ ID NO: 329 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.
- 106.** The nucleic acid of aspect 98, wherein the IL-15/IL-15R α fusion polypeptide comprises SEQ ID NO: 331 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.
- 107.** The nucleic acid of aspect 98, wherein the IL-15/IL-15R α fusion polypeptide comprises SEQ ID NO: 333 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.
- 108.** The nucleic acid of any one of aspects 99-107, wherein the IL-15/IL-15R α fusion polypeptide further comprises a signal peptide directly or indirectly fused to an N terminus of the IL-15/IL-15R α fusion polypeptide.
- 109.** The nucleic acid of aspect 108, wherein the signal peptide is derived from an IgE polypeptide.
- 110.** The nucleic acid of aspect 109, wherein the signal peptide derived from an IgE polypeptide comprises SEQ ID NO: 367 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.
- 111.** A nucleic acid comprising:
- (a) a nucleic acid encoding (i) a T-cell receptor (TCR) comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain and a β chain, or (ii) a TCR comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain without a β chain, and
 - (b) a nucleic acid encoding a fusion polypeptide comprising (i) SEQ ID NO: 367 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about

98%, at least about 99%, or about 100% identical to SEQ ID NO: 367 fused to (ii) an N terminus of an IL-15/IL-15R α fusion polypeptide,

wherein the TCR α chain and the TCR β chain are selected from SEQ ID NO: 15 and 16, 57 and 58, 59 and 60, 61 and 62, 63 and 64, 65 and 66, 67 and 68, 69 and 70, and 71 and 303;

wherein the CD8 α chain is SEQ ID NO: 7, 258, 259, 262, or a variant thereof;
and

wherein, if present, the CD8 β chain is SEQ ID NO: 8, 9, 10, 11, 12, 13, or 14.

112. The nucleic acid of aspect 111, wherein the nucleic acid of (b) encodes SEQ ID NO: 337 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

113. The nucleic acid of aspect 111, wherein the nucleic acid of (b) encodes SEQ ID NO: 339 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

114. The nucleic acid of aspect 111, wherein the nucleic acid of (b) encodes SEQ ID NO: 341 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

115. The nucleic acid of aspect 111, wherein the nucleic acid of (b) encodes SEQ ID NO: 343 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

116. The nucleic acid of aspect 111, wherein the nucleic acid of (b) encodes SEQ ID NO: 345 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

117. The nucleic acid of aspect 111, wherein the nucleic acid of (b) encodes SEQ ID NO: 347 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

118. The nucleic acid of aspect 111, wherein the nucleic acid of (b) encodes SEQ ID NO: 349 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

119. The nucleic acid of aspect 111, wherein the nucleic acid of (b) encodes SEQ ID NO: 351 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

120. The nucleic acid of aspect 111, wherein the nucleic acid of (b) encodes SEQ ID NO: 353 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

121. A nucleic acid comprising: (a) a nucleic acid at least about 80% identical to the nucleic acid of SEQ ID NO: 267, 269, 271, 273, 275, 277, 279, 281, 283, 285, 287, 289, 291, 295, 297, 299, or 301 and (b) a nucleic acid encoding an IL-15/IL-15R α fusion polypeptide.

122. A nucleic acid comprising: (a) a nucleic acid at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the nucleic acid of SEQ ID NO: 267, 269, 271, 273, 275, 277, 279, 281, 283, 285, 287, 289, 291, 295, 297, 299, or 301 and (b) a nucleic acid encoding an IL-15/IL-15R α fusion polypeptide.

123. The nucleic acid of aspect 121 or aspect 122, wherein the nucleic acid encoding an IL-15/IL-15R α fusion polypeptide is selected from (i) SEQ ID NO: 308 or a sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical thereto, directly or indirectly fused to a 5' end of SEQ ID NO: 312 or a sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical thereto, with or without a nucleic acid encoding a linker therebetween; (ii) SEQ ID NO: 308 or a sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical thereto, directly or indirectly fused to a 5' end of SEQ ID NO: 314 or a sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical thereto, with or without a nucleic acid encoding a linker therebetween; or (iii) SEQ ID NO: 308 or a sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical thereto, directly or indirectly fused to a 5' end of SEQ ID NO: 316 or a sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical thereto, with or without a nucleic acid encoding a linker therebetween.

124. The nucleic acid of aspect 123, further comprising a nucleic acid encoding a signal peptide, wherein the nucleic acid encoding the signal peptide is directly or indirectly fused to the 5' end of SEQ ID NO: 308 of any of (i), (ii), or (iii) or to the 5' end of sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 308 of any of (i), (ii), or (iii).

125. The nucleic acid of aspect 124, wherein the signal peptide is derived from an IgE polypeptide.

126. The nucleic acid of aspect 125, wherein the nucleic acid encoding the signal peptide comprises SEQ ID NO: 368 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

127. The nucleic acid of aspect 121 or aspect 122, wherein the nucleic acid encoding an IL-15/IL-15R α fusion polypeptide is selected from SEQ ID NO: 318, 320, 322, 324, 326, 328, 330, 332, or 334 or a sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the nucleic acid of SEQ ID NO: 318, 320, 322, 324, 326, 328, 330, 332, or 334.

128. The nucleic acid of aspect 127, wherein the nucleic acid encoding an IL-15/IL-15R α fusion polypeptide further comprise an nucleic acid encoding a signal peptide, wherein the nucleic acid encoding the signal peptide is directly or indirectly fused to a 5' end of SEQ ID NO: 318, 320, 322, 324, 326, 328, 330, 332, or 334 or a sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the nucleic acid of SEQ ID NO: 318, 320, 322, 324, 326, 328, 330, 332, or 334.

129. The nucleic acid of aspect 128, wherein the signal peptide is derived from an IgE polypeptide.

130. The nucleic acid of aspect 129, wherein the nucleic acid encoding the signal peptide comprises SEQ ID NO: 368 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

131. The nucleic acid of aspect 121 or aspect 122, wherein the nucleic acid encoding an IL-15/IL-15R α fusion polypeptide (i) further comprises a nucleic acid encoding a signal peptide derived from an IgE polypeptide and (ii) is selected from SEQ ID NO: 338, 340, 342, 344, 346, 348, 350, 352, or 354 or a sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the nucleic acid of SEQ ID NO: 338, 340, 342, 344, 346, 348, 350, 352, or 354.

132. The nucleic acid of aspect 121 or aspect 122, wherein the nucleic acid encoding an IL-15/IL-15R α fusion polypeptide is selected from SEQ ID NO: 318, 322, 326, 328, 330, 332, or 334 or a sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the nucleic acid of SEQ ID NO: 318, 322, 326, 328, 330, 332, or 334.

133. The nucleic acid of aspect 132, wherein the nucleic acid encoding an IL-15/IL-15R α fusion polypeptide further comprise an nucleic acid encoding a signal peptide, wherein the nucleic acid encoding the signal peptide is directly or indirectly fused to a 5' end of SEQ ID NO: 318, 322, 326, 328, 330, 332, or 334 or a sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the nucleic acid of SEQ ID NO: 318, 322, 326, 328, 330, 332, or 334.

134. The nucleic acid aspect 133, wherein the signal peptide is derived from an IgE polypeptide.

- 135.** The nucleic acid of aspect 134, wherein the nucleic acid encoding the signal peptide comprises SEQ ID NO: 368 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.
- 136.** The nucleic acid of aspect 121 or aspect 122, wherein the nucleic acid encoding an IL-15/IL-15R α fusion polypeptide (i) further comprises a nucleic acid encoding a signal peptide derived from an IgE polypeptide and (ii) is selected from SEQ ID NO: 338, 342, 346, 348, 350, 352, or 354 or a sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the nucleic acid of SEQ ID NO: 338, 342, 346, 348, 350, 352, or 354.
- 137.** A vector comprising the nucleic acid of any one of aspects 84-136.
- 138.** A vector comprising a nucleic acid encoding at least one CD8 α chain, at least one TCR α chain, at least one TCR β chain, at least one IL-15/IL-15R α fusion polypeptide, and optionally at least one CD8 β chain.
- 139.** A vector comprising N1, N2, N3, N4, N5, L1, L2, L3, and L4, in any order, wherein N1 comprises a nucleic acid encoding a CD8 β chain and is present or absent, N2 comprises a nucleic acid encoding a CD8 α chain, N3 comprises a nucleic acid encoding a TCR β chain, N4 comprises a nucleic acid encoding a TCR α chain, and N5 comprises a nucleic acid encoding an IL-15/IL-15R α fusion polypeptide; and wherein L1-L4 each comprises a nucleic acid encoding at least one linker, wherein each of L1-L4 is independently the same or different, and wherein each of L1-L4 is independently present or absent.
- 140.** The vector of aspect 139 comprising Formula III or Formula IV:
- 5'-N1-L1-N2-L2-N3-L3-N4-L4-N5-3' [III]
- 5'-N5-L1-N1-L2-N2-L3-N3-L4-N4-3' [IV].
- 141.** The vector of aspect 139 or aspect 140, wherein N1 comprises a nucleic acid encoding SEQ ID NO: 8, 9, 10, 11, 12, 13, or 14.
- 142.** The vector of any one of aspects 139-141, wherein N2 comprises a nucleic acid encoding a SEQ ID NO: 7, 258, 259, 262, or a variant thereof.
- 143.** The vector of any one of aspects 139-142, wherein N4 and N3 comprise nucleic acids encoding SEQ ID NO: 15 and 16, 17 and 18, 19 and 20, 21 and 22, 23 and 24, 25 and 26, 27 and 28, 29 and 30, 31 and 32, 33 and 34, 35 and 36, 37 and 38, 39 and 40, 41 and 42, 43 and 44, 45 and 46, 47 and 48, 49 and 50, 51 and 52, 53 and 54, 55 and 56, 57 and 58, 59 and 60, 61 and 62, 63 and 64, 65 and 66, 67 and 68, 69 and 70, 71 and 303, 304 and 74, 75 and 76, 77 and 78, 79 and 80, 81 and 82, 83 and 84, 85 and 86, 87 and 88, 89 and 90, or 91 and 92.
- 144.** The vector of any one of aspects 139-143, wherein N5 comprises a nucleic acid encoding (i) SEQ ID NO: 307 or a sequence at least about 95%, at least about 96%, at least about

97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 307, directly or indirectly fused to an N terminus of SEQ ID NO: 311 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 311, with or without a linker therebetween; (ii) SEQ ID NO: 307 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 307, directly or indirectly fused to an N terminus of SEQ ID NO: 313 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 313, with or without a linker therebetween; or (iii) SEQ ID NO: 307 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 307, directly or indirectly fused to an N terminus of SEQ ID NO: 315 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 315, with or without a linker therebetween.

145. The vector of aspect 144, wherein N5 further comprises a nucleic acid encoding a signal peptide directly or indirectly fused to the 5' end of the nucleic acid encoding SEQ ID NO: 307 of any of (i), (ii), or (iii) or to the 5' end of the nucleic acid encoding the sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 307 of any of (i), (ii), or (iii).

146. The vector of aspect 145, wherein the signal peptide is derived from an IgE polypeptide.

147. The vector of aspect 146, wherein the signal peptide derived from an IgE polypeptide comprises SEQ ID NO: 367 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

148. The vector of any one of aspects 139-143, wherein N5 comprises a nucleic acid encoding SEQ ID NO: 317, 319, 321, 323, 325, 327, 329, 331, or 333 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 317, 319, 321, 323, 325, 327, 329, 331, or 333.

149. The vector of aspect 148, wherein N5 further comprises a nucleic acid encoding a signal peptide directly or indirectly fused to the 5' end of the nucleic acid encoding SEQ ID NO: 317, 319, 321, 323, 325, 327, 329, 331, or 333 or to the 5' end of the nucleic acid encoding the sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 317, 319, 321, 323, 325, 327, 329, 331, or 333.

- 150.** The vector of aspect 149, wherein the signal peptide is derived from an IgE polypeptide.
- 151.** The vector of aspect 150, wherein the signal peptide derived from an IgE polypeptide comprises SEQ ID NO: 367 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.
- 152.** The vector of any one of aspects 139-143, wherein (i) N5 further comprises a nucleic acid encoding a signal peptide derived from an IgE polypeptide and (ii) N5 encodes SEQ ID NO: 337, 339, 341, 343, 345, 347, 349, 351, or 353, or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 337, 339, 341, 343, 345, 347, 349, 351, or 353.
- 153.** The vector of any one of aspects 139-143, wherein N5 comprises a nucleic acid encoding SEQ ID NO: 317, 321, 325, 327, 329, 331, or 333 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 317, 321, 325, 327, 329, 331, or 333.
- 154.** The vector of aspect 153, wherein N5 further comprises a nucleic acid encoding a signal peptide directly or indirectly fused to the 5' end of the nucleic acid encoding SEQ ID NO: 317, 321, 325, 327, 329, 331, or 333 or to the 5' end of the nucleic acid encoding the sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 317, 321, 325, 327, 329, 331, or 333.
- 155.** The vector of aspect 154, wherein the signal peptide is derived from an IgE polypeptide.
- 156.** The vector of aspect 155, wherein the signal peptide derived from an IgE polypeptide comprises SEQ ID NO: 367 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.
- 157.** The vector of any one of aspects 139-143, wherein (i) N5 further comprises a nucleic acid encoding a signal peptide derived from an IgE polypeptide and (ii) N5 encodes SEQ ID NO: 337, 341, 345, 347, 349, 351, or 353 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 337, 341, 345, 347, 349, 351, or 353.
- 158.** The vector of any one of aspects 137-157, wherein (i) the vector further encodes a 2A peptide or an internal ribosome entry site (IRES) positioned between N1 and L1, between L1 and N2, between N2 and L2, between L2 and N3, between N3 and L3, between L3 and N4, between N4 and L4, between L4 and N5, or any combination thereof or (ii) the vector further encodes a 2A peptide or an internal ribosome entry site (IRES) positioned between N5 and L1, between L1

and N1, between N1 and L2, between L2 and N2, between N2 and L3, between L3 and N3, between N3 and L4, between L4 and N4, or any combination thereof.

159. The vector of any one of aspects 137-157, wherein (i) the vector further encodes a furin positioned between N1 and L1, between L1 and N2, between N2 and L2, between L2 and N3, between N3 and L3, between L3 and N4, between N4 and L4, between L4 and N5, or any combination thereof or (ii) the vector further encodes a furin positioned between N5 and L1, between L1 and N1, between N1 and L2, between L2 and N2, between N2 and L3, between L3 and N3, between N3 and L4, between L4 and N4, or any combination thereof.

160. The vector of aspect 158 or aspect 159, wherein the 2A peptide is P2A (SEQ ID NO: 93), T2A (SEQ ID NO: 94), E2A (SEQ ID NO: 95), or F2A (SEQ ID NO: 96).

161. The vector of aspect 154 or aspect 155, wherein the IRES is selected from the group consisting of IRES from picornavirus, IRES from flavivirus, IRES from pestivirus, IRES from retrovirus, IRES from lentivirus, IRES from insect RNA virus, and IRES from cellular mRNA.

162. The vector of any one of aspects 137-161, wherein the vector further encodes a post-transcriptional regulatory element (PRE) sequence selected from a Woodchuck PRE (WPRE) (SEQ ID NO: 264), Woodchuck PRE (WPRE) mutant 1 (SEQ ID NO: 256), Woodchuck PRE (WPRE) mutant 2 (SEQ ID NO: 257), or hepatitis B virus (HBV) PRE (HPRE) (SEQ ID NO: 437).

163. The vector of aspect 162, wherein the post-transcriptional regulatory element (PRE) sequence is a Woodchuck PRE (WPRE) mutant 1 comprising the nucleic acid sequence of SEQ ID NO: 256.

164. The vector of aspect 162, wherein the post-transcriptional regulatory element (PRE) sequence is a Woodchuck PRE (WPRE) mutant 2 comprising the nucleic acid sequence of SEQ ID NO: 257.

165. The vector of any one of aspects 137-164, wherein the vector further comprises a promoter selected from cytomegalovirus (CMV) promoter, phosphoglycerate kinase (PGK) promoter, myelin basic protein (MBP) promoter, glial fibrillary acidic protein (GFAP) promoter, modified MoMuLV LTR comprising myeloproliferative sarcoma virus enhancer (MNDU3), Ubiquitin C promoter, EF-1 alpha promoter, or Murine Stem Cell Virus (MSCV) promoter.

166. The vector of aspect 165, wherein the promoter is a Murine Stem Cell Virus (MSCV) promoter.

167. The vector of any one of aspects 137-166, wherein the vector is a viral vector or a non-viral vector.

168. The vector of aspect 167, wherein the vector is a viral vector.

- 169.** The vector of aspect 168, wherein the viral vector is selected from adenoviruses, poxviruses, alphaviruses, arenaviruses, flaviviruses, rhabdoviruses, retroviruses, lentiviruses, herpesviruses, paramyxoviruses, picornaviruses, and any combination thereof.
- 170.** The vector of aspect 168 or 169, wherein the viral vector is pseudotyped with an envelope protein of a virus selected from the native feline endogenous virus (RD114), a version of RD114 (RD114TR), gibbon ape leukemia virus (GALV), a version of GALV (GALV-TR), amphotropic murine leukemia virus (MLV 4070A), baculovirus (GP64), vesicular stomatitis virus (VSV-G), fowl plague virus (FPV), Ebola virus (EboV), or baboon retroviral envelope glycoprotein (BaEV), and lymphocytic choriomeningitis virus (LCMV).
- 171.** The vector of any one of aspects 137-170, wherein the vector is a lentiviral vector.
- 172.** The vector of any one of aspects 137-171, wherein the vector further comprises a nucleic acid encoding a chimeric antigen receptor (CAR).
- 173.** A T cell and/or natural killer cell transduced with the nucleic acid of any one of aspects 84-136.
- 174.** A T cell and/or natural killer cell transduced with the vector of any one of aspects 137-172.
- 175.** A T cell and/or natural killer cell comprising:
- (a) (i) a T-cell receptor (TCR) comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain and a β chain, or (ii) a TCR comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain without a β chain, and
 - (b) an IL-15/IL-15R α fusion polypeptide,
- wherein the TCR α chain and the TCR β chain are selected from SEQ ID NO: 15 and 16, 17 and 18, 19 and 20, 21 and 22, 23 and 24, 25 and 26, 27 and 28, 29 and 30, 31 and 32, 33 and 34, 35 and 36, 37 and 38, 39 and 40, 41 and 42, 43 and 44, 45 and 46, 47 and 48, 49 and 50, 51 and 52, 53 and 54, 55 and 56, 57 and 58, 59 and 60, 61 and 62, 63 and 64, 65 and 66, 67 and 68, 69 and 70, 71 and 303, 304 and 74, 75 and 76, 77 and 78, 79 and 80, 81 and 82, 83 and 84, 85 and 86, 87 and 88, 89 and 90, and 91 and 92;
- wherein the CD8 α chain is SEQ ID NO: 7, 258, 259, 262, or a variant thereof;
- wherein, if present, the CD8 β chain is SEQ ID NO: 8, 9, 10, 11, 12, 13, or 14;
- and
- wherein the IL-15/IL-15R α fusion polypeptide is selected from (i) SEQ ID NO: 307 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 307, directly or indirectly fused to an N terminus of SEQ ID NO: 311 or a sequence at least about 95%, at

least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 311, with or without a linker therebetween; (ii) SEQ ID NO: 307 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 307, directly or indirectly fused to an N terminus of SEQ ID NO: 313 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 313, with or without a linker therebetween; or (iii) SEQ ID NO: 307 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 307, directly or indirectly fused to an N terminus of SEQ ID NO: 315 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 315, with or without a linker therebetween.

176. The T cell and/or natural killer cell of aspect 175, wherein the IL-15/IL-15R α fusion polypeptide further comprises a signal peptide directly or indirectly fused to the N terminus of SEQ ID NO: 307 of any of (i), (ii), or (iii) or to the N terminus of a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 307 of any of (i), (ii), or (iii).

177. The T cell and/or natural killer cell of aspect 176, wherein the signal peptide is derived from an IgE polypeptide.

178. The T cell and/or natural killer cell of aspect 177, wherein the signal peptide derived from an IgE polypeptide comprises SEQ ID NO: 367 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

179. A T cell and/or natural killer cell comprising:

(a) (i) a T-cell receptor (TCR) comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain and a β chain, or (ii) a TCR comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain without a β chain, and

(b) an IL-15/IL-15R α fusion polypeptide,

wherein the TCR α chain and the TCR β chain are selected from SEQ ID NO: 15 and 16, 17 and 18, 19 and 20, 21 and 22, 23 and 24, 25 and 26, 27 and 28, 29 and 30, 31 and 32, 33 and 34, 35 and 36, 37 and 38, 39 and 40, 41 and 42, 43 and 44, 45 and 46, 47 and 48, 49 and 50, 51 and 52, 53 and 54, 55 and 56, 57 and 58, 59 and 60, 61 and 62, 63 and 64, 65 and 66, 67 and 68, 69 and 70, 71 and 303, 304 and 74, 75 and 76, 77 and 78, 79 and 80, 81 and 82, 83 and 84, 85 and 86, 87 and 88, 89 and 90, and 91 and 92;

wherein the CD8 α chain is SEQ ID NO: 7, 258, 259, 262, or a variant thereof;
 wherein, if present, the CD8 β chain is SEQ ID NO: 8, 9, 10, 11, 12, 13, or 14;
 and

wherein the IL-15/IL-15R α fusion polypeptide is selected from SEQ ID NO: 317, 319, 321, 323, 325, 327, 329, 331, or 333, or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 317, 319, 321, 323, 325, 327, 329, 331, or 333.

180. The T cell and/or natural killer cell of aspect 179, wherein the IL-15/IL-15R α fusion polypeptide further comprises a signal peptide directly or indirectly fused to an N terminus of SEQ ID NO: SEQ ID NO: 317, 319, 321, 323, 325, 327, 329, 331, or 333, or directly or indirectly fused to an N terminus of a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 317, 319, 321, 323, 325, 327, 329, 331, or 333.

181. The T cell and/or natural killer cell of aspect 180, wherein the signal peptide is derived from an IgE polypeptide.

182. The T cell and/or natural killer cell of aspect 181, wherein the signal peptide derived from an IgE polypeptide comprises SEQ ID NO: 367 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

183. A T cell and/or natural killer cell comprising:

(a) (i) a T-cell receptor (TCR) comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain and a β chain, or (ii) a TCR comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain without a β chain, and

(b) a fusion polypeptide comprising (i) a signal peptide comprising SEQ ID NO: 367 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 367 fused to (ii) an IL-15/IL-15R α fusion polypeptide,

wherein the TCR α chain and the TCR β chain are selected from SEQ ID NO: 15 and 16, 17 and 18, 19 and 20, 21 and 22, 23 and 24, 25 and 26, 27 and 28, 29 and 30, 31 and 32, 33 and 34, 35 and 36, 37 and 38, 39 and 40, 41 and 42, 43 and 44, 45 and 46, 47 and 48, 49 and 50, 51 and 52, 53 and 54, 55 and 56, 57 and 58, 59 and 60, 61 and 62, 63 and 64, 65 and 66, 67 and 68, 69 and 70, 71 and 303, 304 and 74, 75 and 76, 77 and 78, 79 and 80, 81 and 82, 83 and 84, 85 and 86, 87 and 88, 89 and 90, and 91 and 92;

wherein the CD8 α chain is SEQ ID NO: 7, 258, 259, 262, or a variant thereof;

wherein, if present, the CD8 β chain is SEQ ID NO: 8, 9, 10, 11, 12, 13, or 14;
and

wherein the fusion polypeptide of (b) is selected from SEQ ID NO: 337, 339, 341, 343, 345, 347, 349, 351, or 353, or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 337, 339, 341, 343, 345, 347, 349, 351, or 353.

184. A T cell and/or natural killer cell transduced to express

(a) (i) a T-cell receptor (TCR) comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain and a β chain, or (ii) a TCR comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain without a β chain, and

(b) an IL-15/IL-15R α fusion polypeptide,

wherein the TCR α chain and the TCR β chain are selected from SEQ ID NO: 15 and 16, 17 and 18, 19 and 20, 21 and 22, 23 and 24, 25 and 26, 27 and 28, 29 and 30, 31 and 32, 33 and 34, 35 and 36, 37 and 38, 39 and 40, 41 and 42, 43 and 44, 45 and 46, 47 and 48, 49 and 50, 51 and 52, 53 and 54, 55 and 56, 57 and 58, 59 and 60, 61 and 62, 63 and 64, 65 and 66, 67 and 68, 69 and 70, 71 and 303, 304 and 74, 75 and 76, 77 and 78, 79 and 80, 81 and 82, 83 and 84, 85 and 86, 87 and 88, 89 and 90, and 91 and 92;

wherein the CD8 α chain is SEQ ID NO: 7, 258, 259, 262, or a variant thereof;

wherein, if present, the CD8 β chain is SEQ ID NO: 8, 9, 10, 11, 12, 13, or 14;
and

wherein the IL-15/IL-15R α fusion polypeptide is selected from SEQ ID NO: 317, 321, 325, 327, 329, 331, or 333 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 317, 321, 325, 327, 329, 331, or 333.

185. The T cell and/or natural killer cell of aspect 184, wherein the IL-15/IL-15R α fusion polypeptide further comprises a signal peptide directly or indirectly fused to an N terminus of SEQ ID NO: SEQ ID NO: 317, 321, 325, 327, 329, 331, or 333, or directly or indirectly fused to an N terminus of a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 317, 321, 325, 327, 329, 331, or 333.

186. The T cell and/or natural killer cell of aspect 185, wherein the signal peptide is derived from an IgE polypeptide.

187. The T cell and/or natural killer cell of aspect 186, wherein the signal peptide derived from an IgE polypeptide comprises SEQ ID NO: 367 or a sequence at least about 95%, at least

about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

188. A T cell and/or natural killer cell comprising:

(a) (i) a T-cell receptor (TCR) comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain and a β chain, or (ii) a TCR comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain without a β chain, and

(b) a fusion polypeptide comprising (i) a signal peptide comprising SEQ ID NO: 367 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 367 directly or indirectly fused to (ii) an IL-15/IL-15R α fusion polypeptide,

wherein the TCR α chain and the TCR β chain are selected from SEQ ID NO: 15 and 16, 17 and 18, 19 and 20, 21 and 22, 23 and 24, 25 and 26, 27 and 28, 29 and 30, 31 and 32, 33 and 34, 35 and 36, 37 and 38, 39 and 40, 41 and 42, 43 and 44, 45 and 46, 47 and 48, 49 and 50, 51 and 52, 53 and 54, 55 and 56, 57 and 58, 59 and 60, 61 and 62, 63 and 64, 65 and 66, 67 and 68, 69 and 70, 71 and 303, 304 and 74, 75 and 76, 77 and 78, 79 and 80, 81 and 82, 83 and 84, 85 and 86, 87 and 88, 89 and 90, and 91 and 92;

wherein the CD8 α chain is SEQ ID NO: 7, 258, 259, 262, or a variant thereof;

wherein, if present, the CD8 β chain is SEQ ID NO: 8, 9, 10, 11, 12, 13, or 14;

and

wherein the fusion polypeptide of (b) is selected from SEQ ID NO: 337, 341, 345, 347, 349, 351, or 353, or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 337, 341, 345, 347, 349, 351, or 353.

189. A T cell and/or natural killer cell comprising:

(a) (i) a T-cell receptor (TCR) comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain and a β chain, or (ii) a TCR comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain without a β chain, and

(b) an IL-15/IL-15R α fusion polypeptide,

wherein the TCR α chain and the TCR β chain are selected from SEQ ID NO: 15 and 16, 57 and 58, 59 and 60, 61 and 62, 63 and 64, 65 and 66, 67 and 68, 69 and 70, and 71 and 303;

wherein the CD8 α chain is SEQ ID NO: 7, 258, 259, 262, or a variant thereof;

and

wherein, if present, the CD8 β chain is SEQ ID NO: 8, 9, 10, 11, 12, 13, or 14.

- 190.** The T cell and/or natural killer cell of aspect 189, wherein the IL-15/IL-15R α fusion polypeptide comprises SEQ ID NO: 317 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.
- 191.** The T cell and/or natural killer cell of aspect 189, wherein the IL-15/IL-15R α fusion polypeptide comprises SEQ ID NO: 319 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.
- 192.** The T cell and/or natural killer cell of aspect 189, wherein the IL-15/IL-15R α fusion polypeptide comprises SEQ ID NO: 321 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.
- 193.** The T cell and/or natural killer cell of aspect 189, wherein the IL-15/IL-15R α fusion polypeptide comprises SEQ ID NO: 323 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.
- 194.** The T cell and/or natural killer cell of aspect 189, wherein the IL-15/IL-15R α fusion polypeptide comprises SEQ ID NO: 325 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.
- 195.** The T cell and/or natural killer cell of aspect 189, wherein the IL-15/IL-15R α fusion polypeptide comprises SEQ ID NO: 327 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.
- 196.** The T cell and/or natural killer cell of aspect 189, wherein the IL-15/IL-15R α fusion polypeptide comprises SEQ ID NO: 329 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.
- 197.** The T cell and/or natural killer cell of aspect 189, wherein the IL-15/IL-15R α fusion polypeptide comprises SEQ ID NO: 331 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.
- 198.** The T cell and/or natural killer cell of aspect 189, wherein the IL-15/IL-15R α fusion polypeptide comprises SEQ ID NO: 333 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.
- 199.** The T cell and/or natural killer cell of any one of aspects 189-198, wherein the IL-15/IL-15R α fusion polypeptide further comprises a signal peptide directly or indirectly fused to an N terminus of the IL-15/IL-15R α fusion polypeptide.
- 200.** The T cell and/or natural killer cell of aspect 199, wherein the signal peptide is derived from an IgE polypeptide.
- 201.** The T cell and/or natural killer cell of aspect 200, wherein the signal peptide derived from an IgE polypeptide comprises SEQ ID NO: 367 or a sequence at least about 95%, at least

about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

202. A T cell and/or natural killer cell comprising:

(a) (i) a T-cell receptor (TCR) comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain and a β chain, or (ii) a TCR comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain without a β chain, and

(b) a fusion polypeptide comprising (i) SEQ ID NO: 367 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 367 fused to (ii) an N terminus of an IL-15/IL-15R α fusion polypeptide,

wherein the TCR α chain and the TCR β chain are selected from SEQ ID NO: 15 and 16, 57 and 58, 59 and 60, 61 and 62, 63 and 64, 65 and 66, 67 and 68, 69 and 70, and 71 and 303;

wherein the CD8 α chain is SEQ ID NO: 7, 258, 259, 262, or a variant thereof; and

wherein, if present, the CD8 β chain is SEQ ID NO: 8, 9, 10, 11, 12, 13, or 14.

203. The T cell and/or natural killer cell of aspect 202, wherein the fusion polypeptide of (b) comprises SEQ ID NO: 337 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

204. The T cell and/or natural killer cell of aspect 202, wherein the fusion polypeptide of (b) comprises SEQ ID NO: 339 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

205. The T cell and/or natural killer cell of aspect 202, wherein the fusion polypeptide of (b) comprises SEQ ID NO: 341 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

206. The T cell and/or natural killer cell of aspect 202, wherein the fusion polypeptide of (b) comprises SEQ ID NO: 343 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

207. The T cell and/or natural killer cell of aspect 202, wherein the fusion polypeptide of (b) comprises SEQ ID NO: 345 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

208. The T cell and/or natural killer cell of aspect 202, wherein the fusion polypeptide of (b) comprises SEQ ID NO: 347 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

- 209.** The T cell and/or natural killer cell of aspect 202, wherein the fusion polypeptide of (b) comprises SEQ ID NO: 349 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.
- 210.** The T cell and/or natural killer cell of aspect 202, wherein the fusion polypeptide of (b) comprises SEQ ID NO: 351 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.
- 211.** The T cell and/or natural killer cell of aspect 202, wherein the fusion polypeptide of (b) comprises SEQ ID NO: 353 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.
- 212.** The T cell and/or natural killer cell of any one of aspects 173-211, wherein the T cell is an $\alpha\beta$ T cell, a $\gamma\delta$ T cell, a natural killer T cell, or any combination thereof.
- 213.** The T cell and/or natural killer cell of aspect 212, wherein the $\alpha\beta$ T cell is a CD4⁺ T cell.
- 214.** The T cell and/or natural killer cell of aspect 212, wherein the $\alpha\beta$ T cell is a CD8⁺ T cell.
- 215.** The T cell and/or natural killer cell of aspect 212, wherein the $\gamma\delta$ T cell is a V γ 9V δ 2⁺ T cell.
- 216.** A composition comprising the T cell and/or natural killer cell of any one of aspects 173-215.
- 217.** The composition of aspect 216, wherein the composition is a pharmaceutical composition.
- 218.** The composition of aspect 216 or aspect 217, wherein the composition further comprises an adjuvant, excipient, carrier, diluent, buffer, stabilizer, or a combination thereof.
- 219.** The composition of aspect 218, wherein the adjuvant is an anti-CD40 antibody, imiquimod, resiquimod, GM-CSF, cyclophosphamide, sunitinib, bevacizumab, atezolizumab, interferon-alpha, interferon-beta, CpG oligonucleotides and derivatives, poly(I:C) and derivatives, RNA, sildenafil, particulate formulations with poly(lactide co-glycolide) (PLG), virosomes, interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-4 (IL-4), interleukin-7 (IL-7), interleukin-12 (IL-12), interleukin-13 (IL-13), interleukin-15 (IL-15), interleukin-21 (IL-21), interleukin-23 (IL-23), or any combination thereof.
- 220.** The composition of aspect 218 or aspect 219, wherein the adjuvant is IL-2, IL-7, IL-12, IL-15, IL-21, or any combination thereof.
- 221.** A method of preparing T cells and/or natural killer cells for immunotherapy comprising:

isolating T cells and/or natural killer cells from a blood sample of a human subject,
activating the isolated T cells and/or natural killer cells,
transducing the activated T cells and/or natural killer cells with the nucleic acid of any one of aspects 84-136 or the vector of any one of aspects 137-172, and
expanding the transduced T cells and/or natural killer cells.

222. The method of aspect 221, further comprising isolating CD4+CD8+ T cells from the transduced T cells and/or natural killer cells and expanding the isolated CD4+CD8+ transduced T cells.

223. The method of aspect 221 or aspect 222, wherein the blood sample comprises peripheral blood mononuclear cells (PMBC).

224. The method of any one of aspects 221-223, wherein the activating comprises contacting the T cells and/or natural killer cells with an anti-CD3 and an anti-CD28 antibody.

225. The method of any one of aspects 221-224, wherein the T cell is a CD4+ T cell.

226. The method of any one of aspects 221-224, wherein the T cell is a CD8+ T cell.

227. The method of aspect 221-226, wherein the T cell is a $\gamma\delta$ T cell or an $\alpha\beta$ T cell.

228. The method of any one of aspects 221-227, wherein the activation, the expanding, or both are in the presence of a combination of IL-2 and IL-15 and optionally with zoledronate.

229. A method of treating a patient who has cancer, comprising administering to the patient the composition of any one of aspects 216-220, wherein the cancer is selected from the group consisting of non-small cell lung cancer, small cell lung cancer, melanoma, liver cancer, breast cancer, uterine cancer, Merkel cell carcinoma, pancreatic cancer, gallbladder cancer, bile duct cancer, colorectal cancer, urinary bladder cancer, kidney cancer, leukemia, ovarian cancer, esophageal cancer, brain cancer, gastric cancer, and prostate cancer.

230. A method of eliciting an immune response in a patient who has cancer, comprising administering to the patient the composition of any one of aspects 216-220, wherein the cancer is selected from the group consisting of non-small cell lung cancer, small cell lung cancer, melanoma, liver cancer, breast cancer, uterine cancer, Merkel cell carcinoma, pancreatic cancer, gallbladder cancer, bile duct cancer, colorectal cancer, urinary bladder cancer, kidney cancer, leukemia, ovarian cancer, esophageal cancer, brain cancer, gastric cancer, and prostate cancer.

231. The method of aspect 229 or 230, wherein the T cell and/or natural killer cell kills cancer cells that present a peptide in a complex with an MHC molecule on a cell surface.

232. A method of increasing persistence, functionality, naivety, longevity, capacity to kill antigen-presenting cells, or a combination thereof, of T cells and/or natural killer cells, comprising:

isolating T cells and/or natural killer cells from a blood sample of a human subject,
activating the isolated T cells and/or natural killer cells,
transducing the activated T cells and/or natural killer cells with the nucleic acid of any one of aspects 40 or 84-136 or the vector of any one of aspects 47-62 or 137-172, or a combination thereof, to obtain transduced T cells and/or natural killer cells, and
obtaining the transduced T cells and/or natural killer cells,
wherein the persistence, longevity, functionality, naivety, capacity to kill antigen-presenting cells, or a combination thereof of the transduced T cells and/or natural killer cells is increased as compared with that of control cells.

233. The method of aspect 232, further comprising expanding the transduced T cells and/or natural killer cells.

234. The method of aspect 232 or aspect 233, wherein the control cells comprise non-transduced T cells and/or natural killer cells, T cells and/or natural killer cells transduced with TCR only, or a combination thereof.

235. The method of aspect 232 or aspect 232, wherein the control cells comprise non-transduced T cells and/or natural killer cells, T cells and/or natural killer cells transduced with TCR only, T cells and/or natural killer cells transduced with TCR and CD8 only, or a combination thereof.

236. The method of any one of aspects 230-235, wherein the persistence, longevity, functionality, naivety, capacity to kill antigen-presenting cells, or a combination thereof of the transduced T cells and/or natural killer cells and control cells is determined after one challenge with antigen-presenting cells, two challenges with antigen-presenting cells, three challenges with antigen-presenting cells, four challenges with antigen-presenting cells, five challenges with antigen-presenting cells, six challenges with antigen-presenting cells, seven challenges with antigen-presenting cells, or more challenges with antigen-presenting cells.

237. The method of any one of aspects 230-235, wherein the persistence, longevity, functionality, naivety, capacity to kill antigen-presenting cells, or a combination thereof of the transduced T cells and/or natural killer cells and control cells is determined after five or more challenges with antigen-presenting cells or more challenges with antigen-presenting cells.

- 238.** A method of increasing interferon γ (IFN γ) secretion by T cells and/or natural killer cells, comprising:
- isolating T cells and/or natural killer cells from a blood sample of a human subject,
 - activating the isolated T cells and/or natural killer cells,
 - transducing the activated T cells and/or natural killer cells with the nucleic acid of any one of aspects 40 or 84-136 or the vector of any one of aspects 47-62 or 137-172, or a combination thereof, to obtain transduced T cells and/or natural killer cells, and
 - obtaining the transduced T cells and/or natural killer cells,
- wherein the IFN γ secretion of the transduced T cells and/or natural killer cells is increased as compared with that of control cells.
- 239.** The method of aspect 238, further comprising expanding the transduced T cells and/or natural killer cells.
- 240.** The method of aspect 238 or aspect 239, wherein the control cells comprise non-transduced T cells and/or natural killer cells, T cells and/or natural killer cells transduced with TCR only, or a combination thereof.
- 241.** The method of aspect 238 or aspect 239, wherein control cells comprise non-transduced T cells and/or natural killer cells, T cells and/or natural killer cells transduced with TCR only, T cells and/or natural killer cells transduced with TCR and CD8 only, or a combination thereof.
- 242.** The method of any one of aspects 238-241, wherein the IFN γ secretion by the transduced T cells and/or natural killer cells and control cells is determined after one challenge with antigen-presenting cells, two challenges with antigen-presenting cells, three challenges with antigen-presenting cells, four challenges with antigen-presenting cells, five challenges with antigen-presenting cells, six challenges with antigen-presenting cells, seven challenges with antigen-presenting cells, or more challenges with antigen-presenting cells.
- 243.** The method of any one of aspects 238-241, wherein the IFN γ secretion by the transduced T cells and/or natural killer cells and control cells is determined after five or more challenges with antigen-presenting cells or more challenges with antigen-presenting cells.
- 244.** The method of any one of aspects 230-243, wherein the antigen presenting cells present an antigen on a cell surface, and the transduced T cells and/or natural killer cells and control cells are capable of killing the antigen presenting cells.
- 245.** The method of aspect 244, wherein the antigen comprises a peptide.

- 246.** The method of aspect 245, wherein the peptide is in a complex with an MHC molecule on the cell surface.
- 247.** A transduced T cell and/or natural killer cell obtained by the method of any one of aspects 230-247.
- 248.** The transduced T cell and/or natural killer cell of aspect 247, wherein the T cell is an $\alpha\beta$ T cell, a $\gamma\delta$ T cell, a natural killer T cell, or any combination thereof.
- 249.** The transduced T cell and/or natural killer cell of aspect 248, wherein the $\alpha\beta$ T cell is a CD4⁺ T cell.
- 250.** The transduced T cell and/or natural killer cell of aspect 248, wherein the $\alpha\beta$ T cell is a CD8⁺ T cell.
- 251.** The transduced T cell and/or natural killer cell of aspect 248, wherein the $\gamma\delta$ T cell is a V γ 9V δ 2⁺ T cell.
- 252.** A composition comprising the transduced T cell and/or natural killer cell of any one of aspects 248-251.
- 253.** The composition of aspect 252, wherein the composition is a pharmaceutical composition.
- 254.** The composition of aspect 252 or aspect 253, wherein the composition further comprises an adjuvant, excipient, carrier, diluent, buffer, stabilizer, or a combination thereof.
- 255.** The composition of aspect 254, wherein the adjuvant is an anti-CD40 antibody, imiquimod, resiquimod, GM-CSF, cyclophosphamide, sunitinib, bevacizumab, atezolizumab, interferon-alpha, interferon-beta, CpG oligonucleotides and derivatives, poly(I:C) and derivatives, RNA, sildenafil, particulate formulations with poly(lactide co-glycolide) (PLG), virosomes, interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-4 (IL-4), interleukin-7 (IL-7), interleukin-12 (IL-12), interleukin-13 (IL-13), interleukin-15 (IL-15), interleukin-21 (IL-21), interleukin-23 (IL-23), or any combination thereof.
- 256.** The composition of aspect 254 or aspect 255, wherein the adjuvant is IL-2, IL-7, IL-12, IL-15, IL-21, or any combination thereof.
- 257.** A method of treating a patient who has cancer, comprising administering to the patient the composition of any one of aspects 252-256, wherein the cancer is selected from the group consisting of non-small cell lung cancer, small cell lung cancer, melanoma, liver cancer, breast cancer, uterine cancer, Merkel cell carcinoma, pancreatic cancer, gallbladder cancer, bile duct cancer, colorectal cancer, urinary bladder cancer, kidney cancer, leukemia, ovarian cancer, esophageal cancer, brain cancer, gastric cancer, and prostate cancer.

258. A method of eliciting an immune response in a patient who has cancer, comprising administering to the patient the composition of any one of aspects 252-256, wherein the cancer is selected from the group consisting of non-small cell lung cancer, small cell lung cancer, melanoma, liver cancer, breast cancer, uterine cancer, Merkel cell carcinoma, pancreatic cancer, gallbladder cancer, bile duct cancer, colorectal cancer, urinary bladder cancer, kidney cancer, leukemia, ovarian cancer, esophageal cancer, brain cancer, gastric cancer, and prostate cancer.

259. The method of aspect 257 or 258, wherein the T cell and/or natural killer cell kills cancer cells that present a peptide in a complex with an MHC molecule on a cell surface.

260. A polypeptide, polypeptides, or fusion polypeptide encoded by the nucleic acid of any one of aspects 1-22, 40 or 84-136.

261. The nucleic acid of any one of aspects 1-22, 40, or 84-136 wherein the nucleic acid is isolated, recombinant, or both isolated and recombinant.

262. The vector of any one of aspects 23-34, 47-62 or 137-172 wherein the vector is isolated, recombinant, or both isolated and recombinant.

263. The T cell and/or natural killer cell of any one of aspects 35-39, 63-67, 173-215, or 248-251 wherein the T cell is isolated, recombinant, engineered, or any combination thereof.

264. The polypeptide, polypeptides, or fusion polypeptide of any one of aspects 41-46 or 260 wherein the polypeptide is isolated, recombinant, or both isolated and recombinant.

CLAIMS

What is claimed is:

1. A nucleic acid encoding a polypeptide comprising SEQ ID NO: 311, 313, or 315 or a polypeptide at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 311, 313, or 315, said nucleic acid optionally comprising SEQ ID NO: 312, 314, or 316 or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 312, 314, or 316.
2. The nucleic acid of claim 1, encoding (i) a polypeptide comprising SEQ ID NO: 307 fused directly or indirectly to an N terminus of a polypeptide comprising any of SEQ ID NO: 311, 313, or 315 or (ii) a polypeptide at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 307 fused directly or indirectly to a polypeptide at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to any of SEQ ID NO: 311, 313, or 315.
3. The nucleic acid of claim 1 or 2 encoding a polypeptide comprising SEQ ID NO: 317, 321, 325, 327, 329, 331, or 333 or a polypeptide at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 317, 321, 325, 327, 329, 331, or 333, the nucleic acid optionally comprising SEQ ID NO: 318, 320, 322, 324, 326, 328, 330, 332, or 334 or a sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the nucleic acid of SEQ ID NO: 318, 320, 322, 324, 326, 328, 330, 332, or 334.
4. The nucleic acid of claim 3, further comprising a nucleic acid encoding a signal peptide directly or indirectly fused to an N terminus of SEQ ID NO: 317, 321, 325, 327, 329, 331, or 333 or to an N terminus of a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 317, 321, 325, 327, 329, 331, or 333.
5. The nucleic acid of claim 4, wherein the signal peptide is derived from an IgE polypeptide and optionally comprises SEQ ID NO: 367 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto, said nucleic acid optionally comprising SEQ ID NO: 368 or a sequence at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical thereto.

6. The nucleic acid of claim 4 or 5, encoding a polypeptide comprising SEQ ID NO: 337, 341, 345, 347, 349, 351, or 353 or a polypeptide at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 337, 341, 345, 347, 349, 351, or 353, said nucleic acid optionally comprising SEQ ID NO: 338, 342, 346, 348, 350, 352, or 354 or a sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 338, 342, 346, 348, 350, 352, or 354.
7. The nucleic acid of any one of claims 1 to 6 further comprising a nucleic acid encoding
- (a) at least one TCR polypeptide comprising an α chain and a β chain,
 - (b) at least one CD8 polypeptide comprising (i) an α chain, (ii) a β chain, or (iii) both an α chain and a β chain, or
 - (c) at least one TCR polypeptide comprising an α chain and a β chain and at least one CD8 polypeptide comprising (i) an α chain, (ii) a β chain, or (iii) both an α chain and a β chain.
8. The nucleic acid of claim 7, comprising a nucleic acid at least about 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the nucleic acid of SEQ ID NO: 267, 269, 271, 273, 275, 277, 279, 281, 283, 285, 287, 289, 291, 295, 297, 299, 301, 438, 439, 440, 441, 442, 443, 444, 445, 446, or 447.
9. The nucleic acid of any one of the preceding claims comprising:
- (a) a nucleic acid encoding
 - (i) a T-cell receptor (TCR) comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain and a β chain, or
 - (ii) a TCR comprising an α chain and a β chain and a CD8 polypeptide comprising an α chain without a β chain, and
 - (b) a nucleic acid encoding a fusion polypeptide according to any one of claims 3 or 6, wherein the TCR α chain and the TCR β chain are selected from SEQ ID NO: 15 and 16, 17 and 18, 19 and 20, 21 and 22, 23 and 24, 25 and 26, 27 and 28, 29 and 30, 31 and 32, 33 and 34, 35 and 36, 37 and 38, 39 and 40, 41 and 42, 43 and 44, 45 and 46, 47 and 48, 49 and 50, 51 and 52, 53 and 54, 55 and 56, 57 and 58, 59 and 60, 61 and 62, 63 and 64, 65 and 66, 67 and 68, 69 and 70, 71 and 303, 304 and 74, 75 and 76, 77 and 78, 79 and 80, 81 and 82, 83 and 84, 85 and 86, 87 and 88, 89 and 90, and 91 and 92;

wherein the CD8 α chain is SEQ ID NO: 7, 258, 259, 262, or a variant thereof;
wherein, if present, the CD8 β chain is SEQ ID NO: 8, 9, 10, 11, 12, 13, or 14.

10. A polypeptide or fusion polypeptide encoded by the nucleic acid of any one of claims 1 to 7.

11. A vector comprising the nucleic acid of any of claims 1 to 9.

12. The vector of claim 11 comprising Formula III or Formula IV:

5'-N1-L1-N2-L2-N3-L3-N4-L4-N5-3' [III]

5'-N5-L1-N1-L2-N2-L3-N3-L4-N4-3' [IV],

wherein

N1 comprises a nucleic acid encoding a CD8 β chain and is present or absent,

N2 comprises a nucleic acid encoding a CD8 α chain,

N3 comprises a nucleic acid encoding a TCR β chain,

N4 comprises a nucleic acid encoding a TCR α chain, and

N5 comprises a nucleic acid encoding an IL-15/IL-15R α fusion polypeptide as
defined in any of claims 1 to 3-6; and

wherein L1-L4 each comprises a nucleic acid encoding at least one linker,

wherein each of L1-L4 is independently the same or different, and wherein
each of L1-L4 is independently present or absent.

13. The vector of any one of claims 11 or 12, wherein the vector is a viral vector or a non-viral vector.

14. The vector of any of claims 11 to 13, wherein the viral vector is selected from adenoviruses, poxviruses, alphaviruses, arenaviruses, flaviviruses, rhabdoviruses, retroviruses, lentiviruses, herpesviruses, paramyxoviruses, picornaviruses, and any combination thereof.

15. The vector of any one of claims 11 to 14, wherein the vector further comprises a nucleic acid encoding a chimeric antigen receptor (CAR).

16. A method of preparing T cells and/or natural killer cells for immunotherapy comprising:
isolating T cells and/or natural killer cells from a blood sample of a human subject,
activating the isolated T cells and/or natural killer cells,
transducing the activated T cells and/or natural killer cells with the nucleic acid of any of
claims 1 to 9 or the vector of any one of claims 11 to 15,
expanding the transduced T cells and/or natural killer cells.

17. The method of claim 16, wherein the blood sample comprises peripheral blood mononuclear cells (PMBC).

18. The method of claim 16 or 17, wherein (i) the activating comprises contacting the T cells and/or natural killer cells with an anti-CD3 and an anti-CD28 antibody; and/or (ii) the activation, the expanding, or both are in the presence of a combination of IL-2 and IL-15 and optionally with zoledronate.

19. A T cell and/or natural killer cell (i) transduced with the nucleic acid of any one of claims 1-9 or (ii) comprising the vector of any one of claims 11 to 15 or (iii) obtained by the method of any one of claim 16 to 18.

20. The T cell and/or natural killer cell of claim 19, wherein the T cell is an $\alpha\beta$ T cell, a $\gamma\delta$ T cell, a natural killer T cell, or any combination thereof.

21. The T cell and/or natural killer cell of claim 19 or 20, wherein the $\alpha\beta$ T cell is a CD4⁺ or CD8⁺ T cell.

22. A composition comprising the T cell and/or natural killer cell of claim 19.

23. The composition of claim 22, wherein the composition is a pharmaceutical composition.

24. The composition of claim 23, wherein the composition further comprises an adjuvant, excipient, carrier, diluent, buffer, stabilizer, or a combination thereof.

25. The composition of claim 24, wherein the adjuvant is an anti-CD40 antibody, imiquimod, resiquimod, GM-CSF, cyclophosphamide, sunitinib, bevacizumab, atezolizumab, interferon-alpha, interferon-beta, CpG oligonucleotides and derivatives, poly(I:C) and derivatives, RNA, sildenafil, particulate formulations with poly(lactide co-glycolide) (PLG), virosomes, interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-4 (IL-4), interleukin-7 (IL-7), interleukin-12 (IL-12), interleukin-13 (IL-13), interleukin-15 (IL-15), interleukin-21 (IL-21), interleukin-23 (IL-23), or any combination thereof.

26. A method of treating and/or eliciting an immune response in a patient who has cancer, comprising administering to the patient the composition of any one of claims 23 to 25, wherein the cancer is selected from the group consisting of non-small cell lung cancer, small cell lung cancer, melanoma, liver cancer, breast cancer, uterine cancer, Merkel cell carcinoma, pancreatic cancer, gallbladder cancer, bile duct cancer, colorectal cancer, urinary bladder cancer, kidney

cancer, leukemia, ovarian cancer, esophageal cancer, brain cancer, gastric cancer, and prostate cancer.

27. The nucleic acid of any one of claims 1 to 9, the polypeptide of claim 10, the vector of any one of claims 11 to 15, the T cell and/or natural killer cell of any one of claims 19 to 21 or the composition of any one of claims 22 to 25 for use as a medicament.

28. The nucleic acid of any one of claims 1 to 9, the polypeptide of claim 10, the vector of any one of claims 11 to 15, the T cell and/or natural killer cell of any one of claims 19 to 21 or the composition of any one of claims 22 to 25 for use in a method of treating cancer, said cancer optionally being selected from the group consisting of non-small cell lung cancer, small cell lung cancer, melanoma, liver cancer, breast cancer, uterine cancer, Merkel cell carcinoma, pancreatic cancer, gallbladder cancer, bile duct cancer, colorectal cancer, urinary bladder cancer, kidney cancer, leukemia, ovarian cancer, esophageal cancer, brain cancer, gastric cancer, and prostate cancer.

29. Use of the nucleic acid of any one of claims 1 to 9, the polypeptide of claim 10, the vector of any one of claims 11 to 15, the T cell and/or natural killer cell of any one of claims 19 to 21 or the composition of any one of claims 22 to 26 in the manufacture of a medicament for the treatment of cancer, said cancer optionally being selected from the group consisting of non-small cell lung cancer, small cell lung cancer, melanoma, liver cancer, breast cancer, uterine cancer, Merkel cell carcinoma, pancreatic cancer, gallbladder cancer, bile duct cancer, colorectal cancer, urinary bladder cancer, kidney cancer, leukemia, ovarian cancer, esophageal cancer, brain cancer, gastric cancer, and prostate cancer.

30. Use of the nucleic acid of any one of claims 1 to 9, the polypeptide of claim 10, the vector of any one of claims 11 to 15, the T cell and/or natural killer cell of any one of claims 19 to 21 or the composition of any one of claims 22 to 26 as a medicament.

31. Use of the nucleic acid of any one of claims 1 to 9, the polypeptide of claim 10, the vector of any one of claims 11 to 15, the T cell and/or natural killer cell of any one of claims 19 to 21 or the composition of any one of claims 22 to 26 for treating cancer, said cancer optionally being selected from the group consisting of non-small cell lung cancer, small cell lung cancer, melanoma, liver cancer, breast cancer, uterine cancer, Merkel cell carcinoma, pancreatic cancer, gallbladder cancer, bile duct cancer, colorectal cancer, urinary bladder cancer, kidney cancer, leukemia, ovarian cancer, esophageal cancer, brain cancer, gastric cancer, and prostate cancer.

32. The nucleic acid, vector, T cell and/or natural killer cell, polypeptide or fusion polypeptide of any one of claims 1 to 15 or 19 to 21, wherein the nucleic acid, vector, T cell and/or natural killer cell, polypeptide or fusion polypeptide is isolated, recombinant, or both isolated and recombinant.