CLAIMS

1. A nucleic acid encoding a polypeptide comprising SEQ ID NO: 313, 311, 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: 313, 311, or 315, said nucleic acid optionally comprising SEQ ID NO: 314, 312, 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: 314, 312, 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: 313, 311, 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: 313, 311, or 315.

3. The nucleic acid of claim 1 or 2 encoding a polypeptide comprising SEQ ID NO: 329, 317, 321, 325, 327, 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: 329, 317, 321, 325, 327, 331, or 333, the nucleic acid optionally comprising SEQ ID NO: 330, 318, 322, 326, 328, 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: 330, 318, 322, 326, 328, 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: 329, 317, 321, 325, 327, 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: 329, 317, 321, 325, 327, 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: 349, 337, 341, 345, 347, 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: 349, 337, 341, 345, 347, 351, or 353, said nucleic acid optionally comprising SEQ ID NO: 350, 338, 342, 346, 348, 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: 350, 338, 342, 346, 348, 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 a TCRα chain and a TCRβ chain,
(b) at least one CD8 polypeptide comprising (i) a CD8α chain, (ii) a CD8β chain, or (iii) both a CD8α chain and a CD8β chain, or
(c) at least one TCR polypeptide comprising a TCRα chain and a TCRβ chain and at least one CD8 polypeptide comprising (i) a CD8α chain, (ii) a CD8β chain, or (iii) both a CD8α chain and a CD8β chain.

8. A polypeptide or fusion polypeptide encoded by the nucleic acid of any one of claims 1-7.

9. A vector comprising the nucleic acid of any one of claims 1-7.

10. The vector of claim 9 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 CD8β chain and is present or absent,

N2 comprises a nucleic acid encoding a CD8α chain,

N3 comprises a nucleic acid encoding a TCRβ chain,

N4 comprises a nucleic acid encoding a TCRα chain, and

N5 comprises a nucleic acid encoding an IL-15/IL-15Rα fusion polypeptide as defined in any one of claims 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.

11. The vector of claim 9 or 10, wherein the vector is a viral vector or a non-viral vector.

12. The vector of any one of claims 9-11, wherein the viral vector is selected from adenoviruses, poxviruses, alphaviruses, arenaviruses, flaviviruses, rhabdoviruses, retroviruses, lentiviruses, herpesviruses, paramyxoviruses, picornaviruses, and any combination thereof.

13. The vector of any one of claims 9-12, wherein the vector further comprises a nucleic acid encoding a chimeric antigen receptor (CAR).

14. 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 claims 1-7 or the vector of any one of claims 9-13,

expanding the transduced T cells and/or natural killer cells.

15. The method of claim 14, wherein the blood sample comprises peripheral blood mononuclear cells (PMBCs).

16. The method of claim 14 or 15, 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.

17. A T cell and/or natural killer cell (i) transduced with the nucleic acid of any one of claims 1-7 or (ii) comprising the vector of any one of claims 9-13 or (iii) obtained by the method of any one of claims 14-16.

18. The T cell and/or natural killer cell of claim 17, wherein the T cell is an αβ T cell, a γδ T cell, a natural killer T cell, or any combination thereof.

19. The T cell and/or natural killer cell of claim 17 or 18, wherein the αβ T cell is a CD4+ T cell or a CD8+ T cell.

20. A composition comprising the T cell and/or natural killer cell of any one of claims 17-19.

21. The composition of claim 20, wherein the composition is a pharmaceutical composition.

22. The composition of claim 21, wherein the composition further comprises an adjuvant, excipient, carrier, diluent, buffer, stabilizer, or a combination thereof.

23. The composition of claim 22, 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.

24. The nucleic acid of any one of claims 1-7, the polypeptide or fusion polypeptide of claim 8, the vector of any one of claims 9-13, the T cell and/or natural killer cell of any one of claims 17-19 or the composition of any one of claims 20-23 for use as a medicament.

25. The nucleic acid of any one of claims 1-7, the polypeptide or fusion polypeptide of claim 8, the vector of any one of claims 9-13, the T cell and/or natural killer cell of any one of claims 17-19 or the composition of any one of claims 20-23 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.

26. Use of the nucleic acid of any one of claims 1-7, the polypeptide or fusion polypeptide of claim 8, the vector of any one of claims 9-13, the T cell and/or natural killer cell of any one of claims 17-19 or the composition of any one of claims 20-23 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.

27. Use of the nucleic acid of any one of claims 1-7, the polypeptide or fusion polypeptide of claim 8, the vector of any one of claims 9-13, the T cell and/or natural killer cell of any one of claims 17-19 or the composition of any one of claims 20-23 as a medicament.

28. The nucleic acid of any one of claims 1-7, the vector of any one of claims 9-13, the T cell and/or natural killer cell of any one of claims 17-19, the polypeptide or fusion polypeptide of

claim 8, wherein the nucleic acid, the vector, the T cell and/or natural killer cell, and the polypeptide or fusion polypeptide is isolated, recombinant, or both isolated and recombinant.