CLAIMS

What is claimed is:

1. A natural killer (NK) cell that expresses all or a functional portion of interleukin-15 (IL-15), wherein either:
(a) all or a functional portion of the IL-15 is fused to all or a portion of a transmembrane protein, wherein the IL-15, or functional portion thereof, is expressed as a membrane-bound polypeptide (mbIL-15) by the NK cell; or
(b) all or a functional portion of the IL-15 is expressed as a secreted polypeptide;
and wherein the NK cell of (a) exhibits enhanced survival and expansion in the absence of IL-2, as compared to an NK cell not expressing mbIL-15 and wherein the NK cell of (b) exhibits enhanced survival and expansion in the absence of IL-2, as compared to an NK cell not expressing secreted IL-15.

2. The NK cell of claim 1 wherein the transmembrane protein is selected from the group consisting of CD8α, CD4, CD3ε, CD3γ, CD3δ, CD3ζ, CD28, CD137, glycophorin A, glycophorin D, nicotinic acetylcholine receptor, a GABA receptor, FcεRIγ, and a T-cell receptor.

3. The NK cell of any one of claims 1 and 2 wherein all or the functional portion of the mbIL-15 is fused to a signal peptide of CD8α and all or a portion of a transmembrane domain of CD8α.

4. The NK cell of any one of claims 1 to 3, wherein the NK cell is CD16 positive.

5. A method of producing a natural killer (NK) cell that expresses all or a functional portion of interleukin-15 (IL-15) comprising:
a) introducing nucleic acid encoding all or a functional portion of IL-15 into the NK cell; and

b) maintaining the NK cell under conditions in which all or a functional portion of the IL-15 is expressed, thereby producing a NK cell that expresses all or a functional portion of IL-15 as a membrane-bound polypeptide (mbIL-15),
wherein expression of all or the functional portion of IL-15 causes the NK cells to exhibit enhanced survival and expansion in the absence of IL-2, as compared to NK cells not expressing mbIL-15.

6. The method of claim 5 wherein the nucleic acid introduced into the NK cell comprises a signal peptide of CD8α, all or a functional portion of IL-15 and all or a portion of the transmembrane domain of CD8α, wherein the nucleic acids comprises SEQ ID NO: 1.

7. The method of any one of claims 5 and 6 wherein the NK cell is transduced with a vector that expresses all or a functional portion of the IL-15 linked (e.g., fused) to all or a portion of the transmembrane domain.

8. The method of claim 7 wherein the vector is a viral vector.

9. A natural killer (NK) cell produced by the method of any one of claims 5 to 8, wherein the NK cell comprises introduced IL-15 or a functional portion thereof and all or a portion of a transmembrane domain of CD8α, resulting in expression of mbIL-15, and wherein the NK cell exhibits enhanced survival and expansion in the absence of IL-2, as compared to NK cells not expressing mbIL15.

10. A composition comprising the NK cell of any one of claims 1 to 4 or 9.

11. A pharmaceutical composition comprising the NK cell of any one of claims 1 to 4 or 9.

12. The pharmaceutical composition of claim 11 further comprising all or a functional portion of IL-2.

13. A natural killer (NK) cell that expresses all or a functional portion of interleukin-15 (IL-15) that is fused to all or a portion of a transmembrane protein, resulting in the IL-15, or functional portion thereof, being expressed as a membrane-bound polypeptide (mbIL-15), wherein the NK cells exhibit enhanced survival and expansion in the absence of IL-2, as compared to NK cells not expressing mbIL-15, for use as a medicament in therapy.

14. The NK cell of claim 13 for use in the treatment of a leukemia (e.g., acute lymphoblastic leukemia; acute myeloid leukemia; chronic myelogenous leukemia, chronic lymphocytic leukemia), a myelodysplastic syndrome, a lymphoma (e.g., B cell non- Hodgkin lymphoma, Hodgkin lymphoma, T-cell lymphoblastic lymphoma, anaplastic large cell lymphoma), a solid tumor (e.g., a breast cancer, prostate cancer, gastric cancer, colon cancer, hepatocellular carcinoma, nasopharyngeal carcinoma, neuroblastoma, high grade glioma), a sarcoma (e.g., Ewing sarcoma, rhabdomyosarcoma, non-rhabdomyosarcoma soft-tissue sarcoma, osteosarcoma).

15. The NK cell of any one of claims 13 and 14, wherein the medicament is suitable for co-administration with interleukin-2 (IL-2).

16. The NK cell of any one of claims 13-15, wherein the medicament is suitable for co-administration with one or more antibodies directed against the cancer.

17. A method of enhancing expansion and/or survival of NK cells comprising:

a) introducing nucleic acid encoding (i) a signal peptide of CD8α, all or a functional portion of IL-15, and all or a portion of a transmembrane domain of CD8α or (ii) all or a functional portion of the IL-15; and

b) maintaining the NK cells under conditions in which all or a functional portion of the IL-15 of (i) or (ii) is expressed and the NK cells proliferate, thereby enhancing expansion and/or survival of the NK cells,

wherein the NK cells of (i) exhibit enhanced survival and expansion in the absence of IL-2, as compared to NK cells not expressing mbIL-15 and wherein the and

wherein the NK cells of (ii) exhibits enhanced survival and expansion in the absence of IL-2, as compared to NK cells not expressing secreted IL-15.

18. The method of claim 17 wherein the nucleic acid introduced into the NK cell comprises a signal peptide of CD8α, all or a functional portion of IL-15 and all or a portion of a transmembrane domain of CD8α, wherein the nucleic acids comprises SEQ ID NO: 1.

19. The method of any one of claims 17 and 18 wherein the NK cell is transduced with a vector that expresses all or a functional portion of the IL-15 linked (e.g., fused) to all or a portion of the transmembrane domain.

20. The method of claim 19 wherein the vector is a retroviral vector.

21. The method of any one of claims 17-20 further comprising contacting the NK cells with IL-2.