We claim:

1. A method of producing natural killer (NK) cells comprising one or more heterologous nucleic acids, comprising:

culturing a population of isolated NK cells in the presence of interleukin-2 (IL-2) for at least two days to produce a population of activated NK cells;

transducing the population of activated NK cells with a viral vector comprising one or more heterologous nucleic acids to produce a population of transduced NK cells, wherein the transducing is performed in the presence of one or more inhibitors of toll-like receptor (TLR) or RIG-I-like receptor (RLR) and/or one or more inhibitors of TBK1/IKKε; and

culturing the population of transduced NK cells in the presence of IL-2 and irradiated feeder cells to produce an expanded population of transduced NK cells.

2. The method of claim 1, wherein:

a) the population of NK cells is cultured in the presence of IL-2 and in the absence of irradiated feeder cells and/or the activated NK cells are transduced with the viral vector in the absence of irradiated feeder cells; or

b) the population of NK cells is cultured in the presence of IL-2 and in the presence of irradiated feeder cells and/or the activated NK cells are transduced with the viral vector in the presence of irradiated feeder cells.

3. The method of claim 1 or claim 2, wherein culturing the population of isolated NK cells in the presence of one or more cytokines comprises culturing the population of isolated NK cells in cell culture medium containing 500 IU/ml IL-2.

4. The method of any one of claims 1 to 3, wherein the population of isolated NK cells is cultured in the presence of IL-2 and no other added cytokines.

5. The method of any one of claims 1 to 4, wherein the one or more inhibitors of TLR and/or RLR and/or one or more inhibitors of TBK1/IKKε is one or more of BX795, 2-

aminopurine, BAY11-7082, Celastrol, CLI-095, H-89, Norharmane, IRAK1/4 inhibitor, MRT67307, AZ13102909, MPI-0485520, Amlexanox, Compound II, and SR8185.

6. The method of claim 5, wherein the one or more inhibitors of TLR and/or RLR and/or one or more inhibitors of TBK1/IKKε is BX795.

7. The method of any one of claims 1 to 6, wherein the viral vector comprising one or more heterologous nucleic acids is a lentivirus vector.

8. The method of claim 7, wherein the lentivirus vector comprises or consists of a nucleic acid sequence with at least 90% sequence identify to any one of SEQ ID NOs: 8-19.

9. The method of any one of claims 1 to 8, wherein the ratio of the irradiated feeder cells to the transduced NK cells is about 10:1.

10. The method of any one of claims 1 to 9, wherein the irradiated feeder cells comprise an Epstein-Barr virus transformed lymphoblastoid cell line or K562 cells.

11. The method of any one of claims 1 to 10, wherein the heterologous nucleic acid encodes:

high affinity CD16 (CD16-V158), CXCR4, CCR7, CXCR3, CD34, double negative TGFβ type II receptor, VLA-4, LFA-1, CD19, or CD4;

a chimeric antigen receptor (CAR) that specifically binds to an antigen expressed on tumor cells, wherein the heterologous nucleic acid encodes a CAR that specifically binds to CD19, CD20, CD33, CD138, CS1, GD2, HER2, erbB2-, CEA, EpCAM, NKG2D-L, or TRAIL-R1;

a nucleic acid molecule encoding a truncated CD34 protein lacking an intracellular domain; and/or

a short hairpin RNA (shRNA), small interfering RNA (siRNA), or an antisense nucleic acid.

12. The method of claim 2, wherein the population of NK cells is cultured in the presence of IL-2 and in the presence of irradiated feeder cells to produce a population of activated NK cells and the feeder cells are substantially separated from the activated NK cells using CD19 immunodepletion and/or CD56 immunoselection.

13. Use of a composition comprising an expanded population of transduced natural killer (NK) cells in the manufacture of a medicament for the treatment of a tumor, hyperproliferative disease, or viral infection in a subject, wherein:

a population of isolated NK cells is obtained from the subject or a donor;

a population of isolated NK cells is cultured in the presence of interleukin-2 (IL-2) for at least two days to produce a population of activated NK cells;

the population of activated NK cells is transduced with a viral vector comprising one or more heterologous nucleic acids to produce a population of transduced NK cells, wherein the transducing is performed in the presence of one or more inhibitors of toll-like receptor (TLR) or RIG-I-like receptor (RLR) and/or one or more inhibitors of TBK1/IKKε;

the population of transduced NK cells is cultured in the presence of IL-2 and irradiated feeder cells to produce the expanded population of transduced NK cells; and

the medicament is to be administered to the subject.

14. The use of claim 13, wherein:

a) the population of NK cells is cultured in the presence of IL-2 and in the absence of irradiated feeder cells; and/or the activated NK cells are transduced with the viral vector in the absence of irradiated feeder cells; or

b) the population of NK cells is cultured in the presence of IL-2 and in the presence of irradiated feeder cells; and/or the activated NK cells are transduced with the viral vector in the presence of irradiated feeder cells.

15. The use of claim 13 or claim 14, wherein culturing the population of isolated NK cells in the presence of one or more cytokines comprises culturing the population of isolated NK cells in cell culture medium containing 500 IU/ml IL-2.

16. The use of any one of claims 13 to 15, wherein the population of isolated NK cells is cultured in the presence of IL-2 and no other added cytokines.

17. The use of any one of claims 13 to 16, wherein the one or more inhibitors of TLR and/or RLR and/or one or more inhibitors of TBK1/IKKε is one or more of BX795, 2-aminopurine, BAY11-7082, Celastrol, CLI-095, H-89, Norharmane, IRAK1/4 inhibitor, MRT67307, AZ13102909, MPI-0485520, Amlexanox, Compound II, and SR8185.

18. The use of claim 17, wherein the one or more inhibitors of TLR and/or RLR and/or one or more inhibitors of TBK1/IKKε is BX795.

19. The use of any one of claims 13 to 18, wherein the viral vector comprising one or more heterologous nucleic acids is a lentivirus vector.

20. The use of claim 19, wherein the lentivirus vector comprises or consists of a nucleic acid sequence with at least 90% sequence identify to any one of SEQ ID NOs: 8-19.

21. The use of claim 19 or claim 20, wherein the lentivirus vector comprises a nucleic acid of interest operably linked to a PGK, EFS, or SV40 promoter.

22. The use of any one of claims 13 to 21, wherein the ratio of the irradiated feeder cells to the transduced NK cells is 10:1.

23. The use of any one of claims 13 to 22, wherein the irradiated feeder cells comprise an Epstein-Barr virus transformed lymphoblastoid cell line or K562 cells.

24. The use of any one of claims 13 to 23, wherein the heterologous nucleic acid encodes:

high affinity CD16 (CD16-V158), CXCR4, CCR7, CXCR3, CD34, double negative TGFβ type II receptor, VLA-4, LFA-1, CD19, or CD4;

a chimeric antigen receptor (CAR) that specifically binds to an antigen expressed on tumor cells, wherein the heterologous nucleic acid encodes a CAR that specifically binds to CD19, CD20, CD33, CD138, CS1, GD2, HER2, erbB2-, CEA, EpCAM, NKG2D-L, or TRAIL-R1;

a nucleic acid molecule encoding a truncated CD34 protein lacking an intracellular domain; and/or

a short hairpin RNA (shRNA), small interfering RNA (siRNA), or an antisense nucleic acid.

25. The use of claim 14, wherein the population of NK cells is cultured in the presence of IL-2 and in the presence of irradiated feeder cells to produce a population of activated NK cells and the feeder cells are substantially separated from the activated NK cells using CD19 immunodepletion and/or CD56 immunoselection.

26. The use of any one of claims 13 to 25, wherein the composition comprising the expanded population of transduced NK cells further comprises a pharmaceutically acceptable carrier.

27. Natural killer cells comprising one or more heterologous nucleic acids produced by the method of any one of claims 1 to 12.

28. A composition comprising natural killer cells comprising one or more heterologous nucleic acids and a pharmaceutically acceptable carrier, wherein the natural killer cells are produced by the method of any one of claims 1 to 12.

29. A method of producing natural killer (NK) cells comprising one or more heterologous nucleic acids, comprising:

culturing a population of isolated NK cells in the presence of interleukin-2 (IL-2) and irradiated feeder cells for at least two days to produce a population of activated NK cells;

transducing the population of activated NK cells with a viral vector comprising one or more heterologous nucleic acids to produce a population of transduced NK cells in the presence of BX795; and

culturing the population of transduced NK cells in the presence of IL-2 and irradiated feeder cells to produce an expanded population of transduced NK cells comprising the one or more heterologous nucleic acids.

30. The method of claim 29, wherein the population of isolated NK cells is cultured in the presence of IL-2 and no other added cytokines.