CLAIMS

What is claimed is:

1. An isolated human NKT cell or a plurality of cells thereof, having reduced or no detectable expression of:

(a) endogenous beta-2-microglobulin (B2M);

(b) endogenous MHC class II-associated invariant chain (Ii); or

(c) both.

2. The cell or cells of claim 1, wherein the cell or cells comprise synthetic DNA or RNA that target the B2M gene or Ii gene.

3. The cell or cells of claim 2, wherein the synthetic DNA or RNA targets the 3' end of the B2M gene or Ii gene.

4. The cell or cells of claim 2 or 3, wherein the synthetic RNA is a shRNA or a CRISPR guide RNA.

5. The cell or cells of any one of claims 1-4, wherein the cell comprises one or more recombinantly engineered receptors.

6. The cell or cells of claim 5, wherein the receptor is a chimeric antigen receptor, chimeric cytokine receptor, or a T cell receptor.

7. The cell or cells of any one of claims 1-6, wherein the cell recombinantly expresses one or more cytokines.

8. The cell or cells of claim 7, wherein the cytokine is IL-15, IL-7, IL-12, IL-18, IL-21, IL-27, IL-33, or a combination thereof.

9. The cell or cells of any one of claims 1-8, further having reduced expression of another endogenous gene besides B2M and/or Ii.

10. The cell or cells of any one of claims 1-9, wherein the cell or cells are NKT cells that are CD62L-positive and/or CD4-positive and/or PD1-negative/low cells.

11. The cell or cells of any one of claims 1-10, wherein the cell or cells are autologous in reference to a subject.

12. The cell or cells of any one of claims 1-10, wherein the cell or cells are allogeneic in reference to a subject.

13. A method of generating the cell or cells of any one of claims 1-12, the method comprising exposing NKT cells to:

(a) one or more agents that reduce expression of endogenous B2M in the cell or cells;

(b) one or more agents that reduce expression of endogenous Ii in the cell or cells; or

(c) both.

14. The method of claim 13, wherein the agent is a DNA vector, morpholinos, siRNA, S-DNA, TALEN, ZFNs, shRNA or a CRISPR guide RNA.

15. The method of claim 13 or 14, wherein the NKT cells are manipulated to express a recombinantly engineered receptor and/or one or more cytokines.

16. A method of treating one or more medical conditions in a subject in need thereof, comprising the step of providing a therapeutically amount of cells of any one of claims 1-12 to the subject.

17. The method of claim 16, wherein the medical condition is cancer or a premalignant condition.

18. The method of claim 17, wherein the cancer is neuroblastoma, breast cancer, cervical cancer, ovary cancer, endometrial cancer, melanoma, bladder cancer, lung cancer, pancreatic cancer, colon cancer, prostate cancer, hematopoietic tumors of lymphoid lineage, leukemia, acute lymphocytic leukemia, chronic lymphocytic leukemia, B-cell lymphoma, Burkitt's lymphoma, multiple myeloma, Hodgkin's lymphoma, Non-Hodgkin's lymphoma, myeloid leukemia, acute myelogenous leukemia (AML), chronic myelogenous leukemia, thyroid cancer, thyroid follicular cancer, tumors of mesenchymal origin, fibrosarcoma, rhabdomyosarcomas, melanoma, uveal melanoma, teratocarcinoma, neuroblastoma, glioma, glioblastoma, benign tumor of the skin, renal cancer, anaplastic large-cell lymphoma, esophageal squamous cells carcinoma,

hepatocellular carcinoma, follicular dendritic cell carcinoma, intestinal cancer, muscle-invasive cancer, seminal vesicle tumor, epidermal carcinoma, spleen cancer, bladder cancer, head and neck cancer, stomach cancer, liver cancer, bone cancer, brain cancer, cancer of the retina, biliary cancer, small bowel cancer, salivary gland cancer, cancer of uterus, cancer of testicles, cancer of connective tissue, prostatic hypertrophy, myelodysplasia, Waldenstrom's macroglobinaemia, nasopharyngeal, neuroendocrine cancer myelodysplastic syndrome, mesothelioma, angiosarcoma, Kaposi's sarcoma, carcinoid, oesophagogastric, fallopian tube cancer, peritoneal cancer, papillary serous mullerian cancer, malignant ascites, gastrointestinal stromal tumor (GIST), or a hereditary cancer syndrome selected from Li-Fraumeni syndrome and Von Hippel-Lindau syndrome (VHL), or wherein the premalignant condition is myelodysplastic syndrome (MDS).

19. The method of claim 17 or 18, wherein the subject has cancer and is provided an additional cancer therapy.

20. The method of claim 19, wherein the additional cancer therapy is surgery, radiation, chemotherapy, immunotherapy, proton therapy, hormone therapy, or a combination thereof.