cells expressing the chimeric receptors, and uses of such host cells for enhancing antibody-based cancer therapy and/or ADCC effects in a subject, *e.g.*, a cancer patient.

In one aspect, the present invention is directed to a chimeric receptor comprising: (a) an extracellular ligand-binding domain of F158 *FCGR3A* or the V158 *FCGR3A* variant; (b) a hinge and transmembrane domains of CD8α; and (c) a cytoplasmic domain comprising a 4-1BB signaling domain and a CD3ζ signaling domain. In one aspect, the present invention is directed to a isolated polynucleotide, comprising a nucleotide sequence encoding the chimeric receptor of the present invention. In one aspect, the present invention is directed to a pharmaceutical composition comprising the polynucleotide of the present invention and a pharmaceutically acceptable carrier or excipient. In one aspect, the present invention is directed to a pharmaceutical composition comprising the polynucleotide of the present invention and a pharmaceutically acceptable carrier or excipient. In one aspect, the present invention is directed to a vector comprising the polynucleotide of the present invention; optionally wherein the polynucleotide is operatively linked to at least one regulatory element for expression of the chimeric receptor encoded by the polynucleotide; and/or, optionally wherein the vector is a viral vector; and, optionally wherein the viral vector is a retroviral vector or a lentiviral vector. In one aspect, the present invention is directed to an isolated host cell, comprising the chimeric receptor of the present invention; optionally wherein the host cell is a T lymphocyte or an NK cell; and, optionally wherein the T lymphocyte or the NK cell is activated and/or expanded *ex vivo*. In one aspect, the present invention is directed to a pharmaceutical composition, comprising the vector of the present invention or a host cell of the present invention, and a pharmaceutically acceptable carrier or excipient; optionally wherein the pharmaceutical composition further comprises an antibody which exerts cytotoxicity to cancer cells; and, optionally wherein the antibody binds to cancer cells and has a human or humanized Fc portion that binds to human CD16, or wherein the antibody is selected from the group consisting of Rituximab, Trastuzumab, hu14.18K322A, Epratuzumab, Cetuximab, and Labetuzumab. In one aspect, the present invention is directed to the use of a T lymphocyte or NK cell expressing the chimeric receptor of the present invention in the manufacture of a medicament for enhancing the efficacy of an antibody-based immunotherapy of a cancer in a subject in need thereof, wherein the subject is being treated with an antibody which binds to cancer cells, and wherein the subject is optionally to be administered with an effective amount of interleukin-2 (IL-2). In one aspect, the present invention is directed to the use of a T lymphocyte or NK cell expressing the chimeric receptor

of the present invention in the manufacture of a medicament for enhancing a T lymphocyte or a NK cell antibody-dependent cell cytotoxicity (ADCC) in a subject; optionally wherein the subject is being treated with an antibody which binds to cancer cells; and/or, optionally wherein the subject is a human patient having a cancer, and/or optionally wherein the subject is to be administered an effective amount of interleukin-2 (IL-2). In one example, the present disclosure provides a chimeric receptor comprising: (a) an extracellular ligand-binding domain of a CD16 molecule; (b) the hinge and transmembrane domains of CD8α; and (c) a cytoplasmic domain comprising a 4-1BB signaling domain and a CD3ζ signaling domain. In some examples, the CD16 molecule is F158 *FCGR3A* and its extracellular ligand-binding domain may comprise (*e.g.*, consists of) the amino acid sequence of SEQ ID NO: 16. In other examples, the CD16 molecule is the V158 *FCGR3A* variant and its extracellular ligand-binding domain may comprise (*e.g.*, consists of) the amino acid sequence of SEQ ID NO: 2.

In any of the chimeric receptors disclosed herein, the hinge and transmembrane domains of CD8α may comprise (*e.g.*, consists of) the amino acid sequence of SEQ ID NO: 3; the 4-1BB signaling domain may comprise (*e.g.*, consists of) the amino acid sequence of SEQ ID NO: 4; and/or the CD3ζ signaling domain may comprise (*e.g.*, consists of) the amino acid sequence of SEQ ID NO: 5.

Any of the chimeric receptors disclosed herein may further comprise a signal peptide of CD8α, which is located at the N-terminus of the chimeric receptor. In one example, such signal peptide of CD8α may comprise (*e.g.*, consists of) the amino acid sequence of SEQ ID NO: 6.

In some examples, the chimeric receptor may comprise the amino acid sequence of residues 22-436 of SEQ ID NO: 1 or residues 22-436 of SEQ ID NO:15. In one example, the the chimeric receptor comprise (*e.g.*, consists of) the amino acid sequence or SEQ ID NO: 1 or SEQ ID NO:15.

In another example, the present disclosure provides an isolated polynucleotide comprising a nucleotide sequence that encodes any of the chimeric receptors disclosed herein. In some examples, the polynucleotide encoding the chimeric receptor may comprise the nucleotide sequence of SEQ ID NO:10 or SEQ ID NO:18, the nucleotide sequence of SEQ ID NO:11, the nucleotide sequence of SEQ ID NO:12, the nucleotide sequence of SEQ ID NO:14, or a combination thereof. In one specific example, the polynucleotide

encoding the chimeric receptor comprises the nucleotide sequence of SEQ ID NO: 9 or SEQ ID NO:17.

In a further example, the present disclosure provides a vector comprising a polynucleotide encoding any of the chimeric receptors disclosed herein, wherein the

polynucleotide may be operatively linked to at least one regulatory element for expression of the chimeric receptor. In one examples, the vector is a viral vector (*e.g.*, a retroviral vector or a lentiviral vector).

Further, the present disclosure provides an isolated host cell comprising any of the chimeric receptors disclosed herein. In one specific example, the host cell is a T lymphocyte or an NK cell. In one specific example, the host cell is a T lymphocyte or an NK cell which is activated and/or expanded *ex vivo* (*e.g.*, T lymphocyte can be activated in the presence of one or more agents selected from the group consisting of anti-CD3/CD28, IL-2, and phytohemoagglutinin; *e.g.*, NK cell can be activated in the presence of one or more agents selected from the group consisting of CD137 ligand protein, CD137 antibody, IL-15 protein, IL-15 receptor antibody, IL-2 protein, IL-12 protein, IL-21 protein, and K562 cell line). In one specific example, the host cell is an autologous T lymphocyte or an autologous NK cell isolated from a patient having a cancer. In one specific example, the host cell is an allogeneic T lymphocyte or an allogeneic NK cell. In one specific example, the host cell is an allogeneic T lymphocyte in which the expression of the endogenous T cell receptor has been inhibited or eliminated.

In yet another example, the present disclosure provides a pharmaceutical composition comprising (i) a polynucleotide encoding any of the chimeric receptors disclosed herein or a vector comprising such a polynucleotide, or a host cell expressing the chimeric receptor; and (ii) a pharmaceutically acceptable carrier or excipient. The pharmaceutical composition may further comprise an antibody, which exerts cytotoxicity to cancer cells (*e.g.*, an antibody which binds to cancer cells and has a human or humanized Fc portion which binds to human CD16, or Rituximab, or Trastuzumab, or hu14.18K322A, or Epratuzumab, or Cetuximab, or Labetuzumab).

In still another example, the present disclosure provides a method for enhancing efficacy of an antibody-based immunotherapy of a cancer in a subject in need thereof. The subject may be treated with an antibody which binds to cancer cells. Such a method may comprise introducing into the subject a therapeutically effective amount of T lymphocytes or NK cells, which express any of the chimeric receptors as described herein.

Moreover, the present disclosure provides a method of enhancing a T lymphocyte or an NK cell antibody-dependent cell cytotoxicity (ADCC) in a subject, the method comprising introducing into the subject a therapeutically effective amount of T lymphocytes or NK cells,

which express the chimeric receptor as disclosed herein. In one specific example, the subject is being treated with an antibody which can bind to cancer cells.

In any of the methods described herein, the subject may be treated with an antibody which may have a human or humanized Fc portion which can bind to human CD16. In one specific example, the subject is being treated with an antibody selected from the group consisting of Rituximab, Trastuzumab, hu14.18K322A, Epratuzumab, Cetuximab, and Labetuzumab. In one specific example, the cancer is selected from the group consisting of carcinomas, lymphomas, sarcomas, blastomas, and leukemias. In one specific example, the cancer is selected from the group consisting of a cancer of B-cell origin (*e.g.*, B-lineage acute lymphoblastic leukemia, B-cell chronic lymphocytic leukemia, B-cell non-Hodgkin's lymphoma), breast cancer, gastric cancer, neuroblastoma, osteosarcoma, lung cancer, melanoma, prostate cancer, colon cancer, renal cell carcinoma, ovarian cancer, rhabdomyosarcoma, leukemia, and Hodgkin's lymphoma. In one specific example, the T lymphocytes or NK cells are autologous T lymphocytes or autologous NK cells isolated from the subject. In one specific example, prior to re-introduction into the subject, the autologous T lymphocytes or autologous NK cells are activated and/or expanded *ex vivo*. In one specific example, the T lymphocytes or NK cells are allogeneic T lymphocytes or allogeneic NK cells. In one specific example, the allogeneic T lymphocytes are T lymphocytes in which the expression of the endogenous T cell receptor has been inhibited or eliminated. In one specific example, prior to introduction into the subject, the allogeneic T lymphocytes or allogeneic NK cells are activated and/or expanded *ex vivo*. In one specific example, the chimeric receptor is introduced into the T lymphocytes or the NK cells by a method selected from the group consisting of retroviral transduction, lentiviral transduction, DNA electroporation, and RNA electroporation.

In any of the methods disclosed herein that involves T lymphocyte activation, the T lymphocytes can be activated in the presence of one or more agents selected from the group consisting of anti-CD3/CD28, IL-2, and phytohemoagglutinin. In any of the methods disclosed herein that involves NK cell activation, NK cells can be activated in the presence of one or more agents selected from the group consisting of CD137 ligand protein, CD137 antibody, IL-15 protein, IL-15 receptor antibody, IL-2 protein, IL-12 protein, IL-21 protein, and K562 cell line.

Any of the methods disclosed herein may further comprise administering to the subject a therapeutically effective amount of IL-2.

What Is Claimed Is:

1. A chimeric receptor comprising: (a) an extracellular ligand-binding domain of F158 *FCGR3A* or the V158 *FCGR3A* variant; (b) a hinge and transmembrane domains of CD8α; and (c) a cytoplasmic domain comprising a 4-1BB signaling domain and a CD3ζ signaling domain.

2. The chimeric receptor of claim 1, wherein the chimeric receptor further comprises a signal peptide of CD8α; and/or,

optionally wherein the extracellular ligand-binding domain of F158 *FCGR3A* and the V158 *FCGR3A* variant consists of the amino acid sequence of SEQ ID NO:16 and SEQ ID NO: 2, respectively; and/or

optionally wherein the hinge and transmembrane domains of CD8α consist of the amino acid sequence of SEQ ID NO: 3; and/or

optionally wherein the 4-1BB signaling domain consists of the amino acid sequence of SEQ ID NO: 4; and/or,

optionally wherein the CD3ζ signaling domain consists of the amino acid sequence of SEQ ID NO: 5; and/or

optionally wherein the signal peptide of CD8α consists of the amino acid sequence of SEQ ID NO: 6.

3. The chimeric receptor of claim 1, which comprises the amino acid sequence of residues 22-436 of SEQ ID NO: 1 or SEQ ID NO:15, or which comprises the amino acid sequence of SEQ ID NO: 1 or SEQ ID NO:15.

4. An isolated polynucleotide, comprising a nucleotide sequence encoding the chimeric receptor of any one of claims 1-3.

5. The isolated polynucleotide of claim 4, which comprises the nucleotide sequence of SEQ ID NO: 10 or SEQ ID NO: 18; and/or

optionally wherein the isolated polynucleotide sequence comprises the nucleotide sequence of SEQ ID NO: 11; and/or

optionally wherein the isolated polynucleotide sequence comprises the nucleotide sequence of SEQ ID NO: 12; and/or

optionally wherein the isolated polynucleotide sequence comprises the nucleotide sequence of SEQ ID NO: 13; and/or

optionally wherein the isolated polynucleotide sequence comprises the nucleotide sequence of SEQ ID NO: 14.

6. The isolated polynucleotide of claim 4, which comprises the nucleotide sequence of SEQ ID NO: 9 or SEQ ID NO: 17.

7. A pharmaceutical composition comprising the polynucleotide of any one of claims 4-6 and a pharmaceutically acceptable carrier or excipient.

8. A vector comprising the polynucleotide of any one of claims 4-6;
optionally wherein the polynucleotide is operatively linked to at least one regulatory element for expression of the chimeric receptor encoded by the polynucleotide; and/or,
optionally wherein the vector is a viral vector; and,
optionally wherein the viral vector is a retroviral vector or a lentiviral vector.

9. An isolated host cell, comprising the chimeric receptor of any one of claims 1-3;
optionally wherein the host cell is a T lymphocyte or an NK cell; and,
optionally wherein the T lymphocyte or the NK cell is activated and/or expanded *ex vivo*.

10. The host cell of claim 9, wherein the T lymphocyte is activated in the presence of one or more agents selected from the group consisting of anti-CD3/CD28, IL-2, and phytohemoagglutinin, or wherein the NK cell is activated in the presence of one or more agents selected from the group consisting of CD137 ligand protein, CD137 antibody, IL-15 protein, IL-15 receptor antibody, IL-2 protein, IL-12 protein, IL-21 protein, and K562 cell line; and/or,
optionally wherein the host cell is an autologous T lymphocyte or an autologous NK cell isolated from a patient having a cancer, or an allogeneic T lymphocyte or an allogeneic NK cell; and,
optionally wherein the endogenous T cell receptor in the allogeneic T lymphocyte has been inhibited or eliminated.

11. A pharmaceutical composition, comprising the vector of claim 8 or a host cell of any one of claims 9 or 10, and a pharmaceutically acceptable carrier or excipient;
optionally wherein the pharmaceutical composition further comprises an antibody which exerts cytotoxicity to cancer cells; and,
optionally wherein the antibody binds to cancer cells and has a human or humanized Fc portion that binds to human CD16, or wherein the antibody is selected from the group

consisting of Rituximab, Trastuzumab, hu14.18K322A, Epratuzumab, Cetuximab, and Labetuzumab.

12. Use of a T lymphocyte or NK cell expressing the chimeric receptor of any one of claims 1-3 in the manufacture of a medicament for enhancing the efficacy of an antibody-based immunotherapy of a cancer in a subject in need thereof, wherein the subject is being treated with an antibody which binds to cancer cells, and wherein the subject is optionally to be administered with an effective amount of interleukin-2 (IL-2).

13. Use of a T lymphocyte or NK cell expressing the chimeric receptor of any one of claims 1-3 in the manufacture of a medicament for enhancing a T lymphocyte or a NK cell antibody-dependent cell cytotoxicity (ADCC) in a subject;
optionally wherein the subject is being treated with an antibody which binds to cancer cells; and/or,
optionally wherein the subject is a human patient having a cancer, and/or
optionally wherein the subject is to be administered an effective amount of interleukin-2 (IL-2).

14. The use according to claim 12 or claim 13, wherein the antibody has a human or humanized Fc portion, which binds to human CD16, or wherein the antibody is selected from the group consisting of Rituximab, Trastuzumab, hu14, 18K322A, Epratuzumab, Cetuximab, and Labetuzumab; and/or
optionally wherein the cancer is selected from the group consisting of carcinoma, lymphoma, sarcoma, blastoma, and leukemia, or wherein the cancer is selected from the group consisting of a cancer of B-cell origin, breast cancer, gastric cancer, neuroblastoma, osteosarcoma, lung cancer, melanoma, prostate cancer, colon cancer, renal cell carcinoma, ovarian cancer, rhabdomyosarcoma, leukemia, and Hodgkin's lymphoma; and,
optionally wherein the cancer of B-cell origin is selected from the group consisting of B-lineage acute lymphoblastic leukemia, B-cell chronic lymphocytic leukemia, and B-cell non-Hodgkin's lymphoma.

15. The use according to any of claims 12 to 14, wherein the T lymphocytes or NK cells are autologous T lymphocytes or autologous NK cells isolated from the subject, the autologous T lymphocytes or NK cells being optionally activated and/or expanded *ex vivo* prior to administering to the subject; or wherein the T lynmphocytes or NK cells are allogeneic T lymphocytes, in which the expression of the endogenous T cell receptor has

been optionally inhibited or eliminated, or allogenic NK cells; the allogenic T lymphocytes or NK cells being optionally activated and/or expanded *ex vivo* prior to administering to the subject.

16. The use according to any of claims 12 to 15, wherein the chimeric receptor is introduced into the T lymphocytes or the NK cells by a method selected from the group consisting of retroviral transduction, lentiviral transduction, DNA electroporation, and RNA electroporation.

17. The use according to claim 15 or claim 16, wherein the T lymphocyte is activated in the presence of one or more agents selected from the group consisting of anti-CD3/CD28, IL-2, and phytohaemoagglutinin, or wherein the NK cell is activated in the presence of one or more agents selected from the group consisting of CD137 ligand protein, CD137 antibody, IL-15 protein, IL-15 receptor antibody, IL-2 protein, IL-12 protein, IL-21 protein, and K562 cell line.