

Patent No. 7,741,465. To this date, none of these chimeric receptors have been adopted for clinical use, and novel designs for antibody-TCR chimeric receptors with improved expression and functionality in human T cells are needed.

[0014] The disclosures of all publications, patents, patent applications and published patent applications referred to herein are hereby incorporated herein by reference in their entirety. PCT Application Number PCT/US2016/058305 is hereby incorporated herein by reference in its entirety.

SUMMARY

[0015] The present application in one example provides immune cells (such as T cells) comprising a chimeric antibody-T cell receptor (TCR) construct (caTCR) and a chimeric signaling receptor (CSR) construct. The caTCR comprises an antigen-binding module that specifically binds to a target antigen and a T cell receptor module (TCRM) capable of recruiting at least one TCR-associated signaling molecule, and the CSR comprises a ligand-binding domain that specifically binds to a target ligand and a co-stimulatory signaling domain capable of providing a stimulatory signal to the immune cell.

[0015a] In one aspect, the present disclosure refers to an immune cell comprising:

a) a chimeric antibody-T cell receptor (TCR) construct (caTCR) comprising:

- i) an antigen binding module that specifically binds to a target antigen;
 - ii) a T cell receptor module (TCRM) comprising a first TCR domain (TCRD) comprising a first TCR transmembrane domain (TCR-TM) and a second TCRD comprising a second TCR-TM, wherein the TCRM facilitates recruitment of at least one TCR-associated signaling molecule; and
 - iii) a stabilization module comprising a first stabilization domain and a second stabilization domain, wherein the first and second stabilization domains have a binding affinity for each other that stabilizes the caTCR, wherein the stabilization module is selected from the group consisting of a C_H1-C_L module, a C_H2-C_H2 module, a C_H3-C_H3 module, and a C_H4-C_H4 module;
- and

b) a chimeric signaling receptor (CSR) comprising:

- i) a ligand-binding module that is capable of binding or interacting with a target ligand;
- ii) a transmembrane module; and
- iii) a co-stimulatory immune cell signaling module that is capable of providing a co-stimulatory signal to the immune cell,

wherein the ligand-binding module and the co-stimulatory immune cell signaling module are not derived from the same molecule, and wherein the CSR lacks a functional primary immune cell signaling domain.

[0016] In some examples, there is provided an immune cell comprising: a) a chimeric antibody-T cell receptor (TCR) construct (caTCR) comprising: i) an antigen binding module that specifically binds to a target antigen; and ii) a T cell receptor module (TCRM) comprising a first TCR domain (TCRD) comprising a first TCR transmembrane domain (TCR-TM) and a second TCRD comprising a second TCR-TM, wherein the TCRM facilitates recruitment of at least one TCR-associated signaling molecule; and b) a chimeric signaling receptor (CSR) comprising: i) a ligand-binding module that is capable of binding or interacting with a target ligand; ii) a transmembrane module; and iii) a co-stimulatory immune cell signaling module that is capable of providing a co-stimulatory signal to the immune cell, wherein the ligand-binding module and the co-stimulatory immune cell signaling module are not derived from the same molecule, and wherein the CSR lacks a functional primary immune cell signaling domain.

[0016a] In one aspect, the present disclosure refers to one or more nucleic acids encoding the caTCR and CSR as disclosed herein, wherein the caTCR and CSR each consist of one or more polypeptide chains encoded by the one or more nucleic acids.

[0017] In some examples, there is provided one or more nucleic acids encoding a caTCR and CSR as described here, wherein the caTCR and CSR each consist of one or more polypeptide chains encoded by the one or more nucleic acids.

[0018] In some examples, there is provided one or more nucleic acids encoding: a) a chimeric antibody-T cell receptor (TCR) construct (caTCR) comprising: i) an antigen binding module that specifically binds to a target antigen; and ii) a T cell receptor module (TCRM)

comprising a first TCR domain (TCRD) comprising a first TCR transmembrane domain (TCR-TM) and a second TCRD comprising a second TCR-TM, wherein the TCRM facilitates recruitment of at least one TCR-associated signaling molecule, and wherein the caTCR consists of one or more polypeptide chains; and b) a chimeric signaling receptor (CSR) comprising: i) a ligand-binding module that is capable of binding or interacting with a target ligand; ii) a transmembrane module; and iii) a co-stimulatory immune cell signaling module that is capable of providing a co-stimulatory signal to the immune cell, wherein the ligand-binding module and the co-stimulatory immune cell signaling module are not derived from the same molecule, wherein the CSR lacks a functional primary immune cell signaling domain, and wherein the CSR consists of one or more polypeptide chains.

[0018a] In one aspect, the present disclosure refers to one or more vectors comprising the one or more nucleic acids as disclosed herein.

[0019] In some examples, there is provided one or more vectors comprising one or more nucleic acids as described herein.

[0020] In some examples, there is provided a composition comprising one or more nucleic acids or one or more vectors as described herein.

[0020a] In one aspect, the present disclosure refers to an immune cell comprising the one or more nucleic acids as disclosed herein, the one or more vectors as disclosed herein.

[0021] In some examples, there is provided an immune cell comprising one or more nucleic acids or one or more vectors as described herein.

[0021a] In one aspect, the present disclosure refers to a pharmaceutical composition comprising the immune cell as disclosed herein, and a pharmaceutically acceptable carrier.

[0022] In some examples, there is provided a pharmaceutical composition comprising an immune cell as described herein, and a pharmaceutically acceptable carrier.

[0022a] In one aspect, the present disclosure refers to use of the immune cell as disclosed herein in the manufacture of a medicament for killing a target cell presenting a target antigen (or treating a target antigen-associated disease).

[0023] In some examples, there is provided a method of killing a target cell presenting a target antigen, comprising contacting the target cell with an immune cell as described herein.

[0023a] In one aspect, the present disclosure refers to use of the pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating a target antigen-associated disease in an individual in need thereof.

[0024] In some examples, there is provided a method of treating a target antigen-associated disease in an individual in need thereof, comprising administering to the individual an effective amount of a pharmaceutical composition as described herein.

[0024a] In one aspect, the present disclosure refers to use of the one or more nucleic acids as disclosed herein or the one or more vectors as disclosed herein in the manufacture of a medicament for providing a co-stimulatory signal to an immune cell comprising a caTCR or transduced with a nucleic acid encoding a caTCR.

[0025] In some examples, there is provided a method of providing a co-stimulatory signal to an immune cell comprising a caTCR or transduced with a nucleic acid encoding a caTCR, comprising introducing into said cell one or more nucleic acids or one or more vectors as described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0026] FIG. 1 shows a schematic representation of several caTCR molecules having different antigen-binding modules.

CLAIMS

What is claimed is:

1. An immune cell comprising:
 - a) a chimeric antibody-T cell receptor (TCR) construct (caTCR) comprising:
 - i) an antigen binding module that specifically binds to a target antigen;
 - ii) a T cell receptor module (TCRM) comprising a first TCR domain (TCRD) comprising a first TCR transmembrane domain (TCR-TM) and a second TCRD comprising a second TCR-TM, wherein the TCRM facilitates recruitment of at least one TCR-associated signaling molecule; and
 - iii) a stabilization module comprising a first stabilization domain and a second stabilization domain, wherein the first and second stabilization domains have a binding affinity for each other that stabilizes the caTCR, wherein the stabilization module is selected from the group consisting of a C_H1-C_L module, a C_H2-C_H2 module, a C_H3-C_H3 module, and a C_H4-C_H4 module; and
 - b) a chimeric signaling receptor (CSR) comprising:
 - i) a ligand-binding module that is capable of binding or interacting with a target ligand;
 - ii) a transmembrane module; and
 - iii) a co-stimulatory immune cell signaling module that is capable of providing a co-stimulatory signal to the immune cell,wherein the ligand-binding module and the co-stimulatory immune cell signaling module are not derived from the same molecule, and wherein the CSR lacks a functional primary immune cell signaling domain.
2. The immune cell of claim 1, wherein the CSR lacks any primary immune cell signaling sequences.
3. The immune cell of claim 1 or 2, wherein the target antigen is a cell surface antigen.
4. The immune cell of claim 1 or 2, wherein the target antigen is a complex comprising a peptide and a major histocompatibility complex (MHC) protein.
5. The immune cell of any one of claims 1-4, wherein the first TCR-TM is derived from one of the transmembrane domains of a first T cell receptor and the second TCR-TM is derived from the other transmembrane domain of the first T cell receptor.
6. The immune cell of claim 5, wherein at least one of the TCR-TMs is non-naturally occurring.

7. The immune cell of claim 5 or 6, wherein the first T cell receptor is a γ/δ T cell receptor.
8. The immune cell of any one of claims 1-7, wherein the antigen-binding module is multispecific.
9. The immune cell of any one of claims 1-8, wherein the target antigen and the target ligand are the same.
10. The immune cell of any one of claims 1-8, wherein the target antigen and the target ligand are different.
11. The immune cell of claim 10, wherein the target ligand is a ligand expressed on the surface of a cell presenting the target antigen.
12. The immune cell of any one of claims 1-11, where the target ligand is a disease-associated ligand.
13. The immune cell of claim 12, wherein the target ligand is a cancer-associated ligand.
14. The immune cell of claim 12, wherein the target ligand is a virus-associated ligand.
15. The immune cell of any one of claims 1-11, where the target ligand is an immunomodulatory molecule.
16. The immune cell of claim 15, wherein the immunomodulatory molecule is an immunosuppressive receptor, and the CSR is an antagonist of the immunosuppressive receptor.
17. The immune cell of claim 15, wherein the immunomodulatory molecule is an immunostimulatory receptor, and the CSR is an agonist of the immunostimulatory receptor.
18. The immune cell of claim 15, where the target ligand is an immune checkpoint molecule.
19. The immune cell of claim 15, wherein the target ligand is an inhibitory cytokine.
20. The immune cell of any one of claims 1-11, where the target ligand is an apoptotic molecule.
21. The immune cell of any one of claims 1-20, wherein the ligand-binding module is an antibody moiety.
22. The immune cell of any one of claims 1-20, wherein the ligand-binding module is derived from the extracellular domain of a receptor.
23. The immune cell of any one of claims 1-22, wherein the transmembrane module of the CSR comprises transmembrane domains derived from CD28, CD3 ϵ , CD3 ζ , CD45, CD4, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137, or CD154.
24. The immune cell of any one of claims 1-23, wherein the co-stimulatory immune cell signaling module is derived from the intracellular domain of a co-stimulatory receptor of a TCR.

25. The immune cell of claim 24, wherein the co-stimulatory receptor is selected from the group consisting of CD28, 4-1BB, OX40, ICOS, CD27, and CD40.
26. The immune cell of any one of claims 1-25, wherein the expression of the CSR is inducible.
27. The immune cell of claim 26, wherein the expression of the CSR is inducible upon activation of the immune cell.
28. The immune cell of any one of claims 1-27, wherein the antigen-binding module of the caTCR comprises an antibody moiety that binds to CD19, wherein the ligand-binding module of the CSR comprises an scFv that binds to CD19, and wherein the transmembrane module and co-stimulatory immune cell signaling module are both derived from CD28.
29. The immune cell of any one of claims 1-27, wherein the antigen-binding module of the caTCR comprises an antibody moiety that binds to AFP, wherein the ligand-binding module of the CSR comprises an scFv that binds to GPC3, and wherein the transmembrane module and co-stimulatory immune cell signaling module are both derived from CD28.
30. The immune cell of any one of claims 1-27, wherein the antigen-binding module of the caTCR comprises an antibody moiety that binds to CD19, wherein the ligand-binding module of the CSR comprises an scFv that binds to CD20, and wherein the transmembrane module and co-stimulatory immune cell signaling module are both derived from CD28.
31. One or more nucleic acids encoding the caTCR and CSR of any one of claims 1-30, wherein the caTCR and CSR each consist of one or more polypeptide chains encoded by the one or more nucleic acids.
32. One or more vectors comprising the one or more nucleic acids of claim 31.
33. An immune cell comprising the one or more nucleic acids of claim 31, the one or more vectors of claim 32.
34. The immune cell of any one of claims 1-30, wherein the immune cell is selected from the group consisting of a cytotoxic T cell, a helper T cell, a natural killer T cell, and a suppressor T cell.
35. A pharmaceutical composition comprising the immune cell of any one of claims 1-30, and a pharmaceutically acceptable carrier.
36. Use of the immune cell of any one of claims 1-30 in the manufacture of a medicament for killing a target cell presenting a target antigen (or treating a target antigen-associated disease).

37. Use of the pharmaceutical composition of claim 35 in the manufacture of a medicament for treating a target antigen-associated disease in an individual in need thereof.
38. Use of the one or more nucleic acids of claim 31 or the one or more vectors of claim 32 in the manufacture of a medicament for providing a co-stimulatory signal to an immune cell comprising a caTCR or transduced with a nucleic acid encoding a caTCR.