

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.

[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. 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; 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, wherein the caTCR further comprises a stabilization module comprising a first stabilization domain and a second stabilization domain, and 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; wherein the immune cell is a T cell or a natural killer (NK) cell.

[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. 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.

[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)

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; 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, wherein the caTCR further comprises a stabilization module comprising a first stabilization domain and a second stabilization domain, and 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;wherein the immune cell is a T cell or a natural killer (NK) cell.
2. The immune cell of claim 1, wherein the CSR lacks any primary immune cell signaling sequences.
3. The immune cell of claim 1, wherein the target antigen is a cell surface antigen.
4. The immune cell of claim 1, wherein the target antigen is a complex comprising a peptide and a major histocompatibility complex (MHC) protein.
5. The immune cell of claim 1, 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, wherein the first T cell receptor is a γ/δ T cell receptor.

8. The immune cell of claim 1, wherein the antigen-binding module is multispecific.
9. The immune cell of claim 1, wherein the target antigen and the target ligand are the same.
10. The immune cell of claim 1, 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 claim 1, 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 1, wherein the ligand-binding module is an antibody moiety.
15. The immune cell of claim 1, wherein the transmembrane module of the CSR comprises transmembrane domains derived from CD28, CD3 ϵ , CD3 ζ , CD45, CD4, CD5, CD8, CD9, CD16, CD22, CD30, CD33, CD37, CD64, CD80, CD86, CD134, CD137, or CD154.
16. The immune cell of claim 1, wherein the co-stimulatory immune cell signaling module is derived from the intracellular domain of a co-stimulatory receptor of a TCR.
17. The immune cell of claim 16, wherein the co-stimulatory receptor is CD28.
18. The immune cell of claim 16, wherein the co-stimulatory receptor is 4-1BB.
19. The immune cell of claim 16, wherein the co-stimulatory receptor is OX40.
20. The immune cell of claim 16, wherein the co-stimulatory receptor is ICOS.
21. The immune cell of claim 16, wherein the co-stimulatory receptor is CD27.
22. The immune cell of claim 16, wherein the co-stimulatory receptor is CD30.
23. The immune cell of claim 16, wherein the co-stimulatory receptor is CD40.
24. One or more nucleic acids encoding the caTCR and CSR of claim 1, wherein the caTCR and CSR each consist of one or more polypeptide chains encoded by the one or more nucleic acids.
25. An immune cell comprising the one or more nucleic acids of claim 24.
26. An *in vitro* method of killing a target cell presenting a target antigen, comprising contacting the target cell with the immune cell of claim 1.
27. Use of the immune cell of claim 1 in the manufacture of a pharmaceutical composition for treating a target antigen-associated disease in an individual in need thereof, wherein the pharmaceutical composition comprises the immune cell of claim 1 and a pharmaceutically acceptable carrier.

28. Use of the immune cell of claim 1 in the manufacture of a medicament for killing a target cell presenting a target antigen, wherein the target cell is to be contacted with the immune cell.