

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.

[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)

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.

[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.

[0021] In some examples, there is provided an immune cell comprising one or more nucleic acids or one or more vectors as described herein. In one aspect, the present disclosure refers to an immune cell comprising the one or more nucleic acids as disclosed herein.

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

[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. In one aspect, the present disclosure refers to an *in vitro* method of killing a target cell presenting a target antigen, comprising contacting the target cell with the immune cell as disclosed herein. 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, wherein the target cell is to be contacted with the immune cell.

[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. In one aspect, the present disclosure refers to use of the immune cell as disclosed herein 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 as disclosed herein and a pharmaceutically acceptable carrier.

[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.