SUMMARY

[0015] The present application in one example provides a construct (such as an isolated construct) comprising an antigen-binding module (such as an antibody moiety) fused to a T cell receptor module (said construct also referred to herein as a "chimeric antibody-TCR molecule," or "caTCR"). In some examples, 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. In some examples, the target antigen is a complex comprising a peptide and an MHC protein (such as an MHC class I protein or an MHC class II protein). In some examples, the target antigen is a cell-surface antigen.

[0016] In some examples, there is provided a chimeric antibody-T cell receptor (TCR) construct (caTCR) comprising an antigen-binding module that specifically binds to a target antigen and 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 at least one of the TCR-TMs is non-naturally occurring, wherein the TCRM facilitates recruitment of at least one TCR-associated signaling molecule, and wherein the antigen-binding module is not a naturally occurring T cell receptor antigen-binding moiety.

[0017] In some examples, there is provided a caTCR comprising: a) a multispecific (*e.g.*, bispecific) antigen-binding module comprising a first antigen-binding domain that specifically binds to a first target antigen and a second antigen-binding domain that specifically binds to a second target antigen; and b) a TCRM comprising a first TCRD (TCRD1) comprising a first TCR-TM and a second TCRD (TCRD2) comprising a second TCR-TM; wherein the TCRM facilitates recruitment of at least one TCR-associated signaling molecule. In some examples, at least one of the TCR-TMs is non-naturally occurring. In some examples, the first TCR-TM and the second TCR-TM are naturally occurring.

[0017a] In one aspect, the present disclosure refers to a chimeric antibody-T cell receptor (TCR) construct (caTCR) comprising: a) a multispecific antigen-binding module comprising a first antigen-binding domain that specifically binds to a first target antigen and a second antigen-binding domain that specifically binds to a second target antigen; b) a TCR module (TCRM), wherein the TCRM comprises a first TCR domain (TCRD) (TCRD1) comprising a first TCR transmembrane domain (TCR-TM) and a second TCRD (TCRD2) comprising a second TCR-TM; wherein the TCRM facilitates recruitment of at least one TCR-associated signaling molecule; and c) a stabilization module, wherein the stabilization module comprises a first stabilization domain comprising a first immunoglobulin constant domain, and a second stabilization domain comprising a second immunoglobulin constant domain; wherein the multispecific antigen-binding module is fused to the N-terminus of the stabilization module, and the stabilization module is fused to the N-terminus of the TCRM.

[0018] In some examples, there is provided one or more nucleic acids encoding a caTCR described herein. In one aspect, the present disclosure refers to one or more nucleic acids encoding the caTCR as disclosed herein. In some examples, there is provided one or more vectors comprising the one or more nucleic acids. In some examples, there is provided a composition comprising the one or more nucleic acids or the one or more vectors. In some examples, there is provided an effector cell comprising the one or more nucleic acids or the one or more vectors. In one aspect, the present disclosure refers to an effector cell presenting on its surface the caTCR as disclosed herein.

[0019] In some examples, there is provided a complex comprising caTCR as described herein and at least one TCR-associated signaling molecule selected from the group consisting of CD3δε, CD3γε, and ζζ. In one aspect, the present disclosure refers to a complex comprising the caTCR as disclosed herein and at least one TCR-associated signaling molecule selected from the group consisting of CD3δε, CD3γε, and ζζ.

[0020] In some examples, there is provided a composition, such as a pharmaceutical composition, comprising an effector cell described herein.

[0021] In some examples, there is provided a method of killing a target cell presenting a target antigen, comprising contacting the target cell with an effector cell 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 effector cell as disclosed herein, wherein the caTCR specifically binds to the target antigen. In one aspect, the present disclosure refers to use of the effector 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 effector cell, wherein the caTCR specifically binds to the target antigen.

[0022] 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 described herein. In one aspect, the present disclosure refers to use of the effector 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 a pharmaceutically acceptable carrier, and wherein the caTCR specifically binds to the target antigen.

[0023] In some examples, there is provided a method of enriching a heterogeneous cell population for an effector cell described herein, comprising: a) contacting the heterogeneous cell population with a ligand comprising the target antigen or one or more epitopes contained therein to form complexes of the effector cell bound to the ligand; and b) separating the complexes from the heterogeneous cell population, thereby generating a cell population enriched for the effector cell.

[0024] In some examples, there is provided a nucleic acid library comprising sequences encoding a plurality of caTCRs as described herein. In some examples, there is provided a method of screening a library described herein for caTCRs having high affinity for a target antigen, comprising: a) introducing the nucleic acid library into a plurality of cells, such that the caTCRs are expressed on the surface of the plurality of cells; b) incubating the plurality of cells with a ligand comprising the target antigen or one or more epitopes contained therein; c) collecting cells bound to the ligand; and d) isolating sequences encoding the caTCRs from cells collected in step c), thereby identifying caTCRs specific for the target antigen.

BRIEF DESCRIPTION OF THE DRAWINGS

[0025] FIG. 1 shows a schematic representation of several caTCR molecules having different antigen-binding modules.

[0026] FIG. 2 shows a schematic representation of the caTCR-1-0 construct, highlighting its transmembrane region that was mutated to create the TM mutants.

[0027] FIG. 3 shows a helical wheel projection of the caTCR transmembrane region. Amino acid positions mutated to make transmembrane mutants are highlighted.

[0028] FIG. 4 shows the expression of the caTCR transmembrane mutants and CD3 on JRT3.1 cells as a percentage of the respective MFI expression on cells transduced with caTCR-1-0 with an anti-AFP158/HLA- A*2:01 binding moiety. Flow cytometry analysis of surface CD3ε or caTCR receptor was used to calculate the MFI of each respective receptor.