

TFP molecule are administered in combination with an agent that treats the disease associated with CD19 or BCMA.

[0039] In one aspect, an isolated nucleic acid molecule provided herein, an isolated polypeptide molecule provided herein, an isolated TFP provided herein, a complex provided herein, a vector provided herein, or a cell provided herein, is for use as a medicament.

[0040] In one aspect, provided herein is a method of treating a mammal having a disease associated with expression of CD19 or BCMA comprising administering to the mammal an effective amount of a TFP molecule provided herein, a cell provided herein, or a polypeptide molecule provided herein, wherein less cytokines are released in the mammal compared a mammal administered an effective amount of a T-cell expressing an anti-CD19 chimeric antigen receptor (CAR) or an anti-BCMA CAR.

[0040a] In one aspect, provided herein is a pharmaceutical composition comprising (I) a T cell from a human subject, wherein the T cell comprises a recombinant nucleic acid molecule encoding a T-cell receptor (TCR) fusion protein (TFP) comprising

- (a) a TCR subunit comprising
 - (i) at least a portion of a TCR extracellular domain,
 - (ii) a TCR transmembrane domain, and
 - (iii) a TCR intracellular domain comprising a stimulatory domain from an intracellular signaling domain of CD3 epsilon, CD3 gamma, or CD3 delta; and
- (b) a murine, human or humanized scFv or single domain antibody comprising an antigen binding domain;

wherein the TCR subunit and the antibody domain are operatively linked, wherein the TFP incorporates into a TCR when expressed in a T-cell, and wherein the T cell exhibits increased cytotoxicity to a human cell expressing an antigen that specifically interacts with the antigen binding domain compared to a T cell not containing the TFP; and

(II) a pharmaceutically acceptable carrier.

[0040b] In one aspect, provided herein is a use of an effective amount of the pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating a mammal having a disease.

INCORPORATION BY REFERENCE

[0041] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0042] FIG. 1 is a schematic illustration demonstrating the use of T-cell receptor fusion polypeptides (TFPs) of the invention. An exemplary TFP contains an anti-CD19 scFv and a full-length CD3 epsilon polypeptide fused via a $(G_4S)_3$ linker sequence. When produced by or introduced into a T-cell, the TFP associates with other polypeptides of the endogenous T-cell receptor (TCR) (shown to include two CD3 epsilon polypeptides, one CD3 gamma polypeptide, one CD3 delta polypeptide, two CD3 zeta polypeptides, one TCR alpha subunit and one TCR beta subunit, where the horizontal grey segment represents the plasma membrane) to form a reprogrammed TCR in which one or both of the endogenous CD3 epsilon polypeptides are substituted by the TFP.

[0043] FIG. 2A represents schematic illustrations demonstrating exemplary variations of reprogrammed T-cell receptor fusion polypeptides (TFPs) of the invention.

[0044] Figure 2A illustrates an exemplary reprogrammed TCR containing a TFP that contains an anti-CD19 scFv and a full-length TCR $V\alpha$ polypeptide fused via a $(G_4S)_3$ linker sequence.

CLAIMS

1. A pharmaceutical composition comprising
 - (I) a T cell from a human subject, wherein the T cell comprises a recombinant nucleic acid molecule encoding a T-cell receptor (TCR) fusion protein (TFP) comprising
 - (a) a TCR subunit comprising
 - (i) at least a portion of a TCR extracellular domain,
 - (ii) a TCR transmembrane domain, and
 - (iii) a TCR intracellular domain comprising a stimulatory domain from an intracellular signaling domain of CD3 epsilon, CD3 gamma, or CD3 delta; and
 - (b) a murine, human or humanized scFv or single domain antibody comprising an antigen binding domain;wherein the TCR subunit and the antibody domain are operatively linked, wherein the TFP incorporates into a TCR when expressed in a T-cell, and wherein the T cell exhibits increased cytotoxicity to a human cell expressing an antigen that specifically interacts with the antigen binding domain compared to a T cell not containing the TFP; and
 - (II) a pharmaceutically acceptable carrier.
2. The pharmaceutical composition of claim 1, wherein the antigen binding domain is an anti-CD19 binding domain or an anti-B-cell maturation antigen (BCMA) binding domain.
3. The pharmaceutical composition of claim 1 or 2, wherein the encoded antigen binding domain is connected to the TCR extracellular domain by a linker sequence, optionally, wherein the encoded linker sequence comprises $(G_4S)_n$, wherein $n=1$ to 4.
4. The pharmaceutical composition of any one of claims 1-3, wherein the TCR subunit comprises (i) a TCR extracellular domain, (ii) a TCR transmembrane domain, and (iii) a TCR intracellular domain, wherein at least two of (i), (ii), and (iii) are from the same TCR subunit, optionally, wherein (i), (ii), and (iii) are from the same TCR subunit.
5. The pharmaceutical composition of any one of claims 1-4, wherein the human or humanized antibody domain comprises a scFv or a single domain antibody, wherein the single domain antibody is optionally a V_H domain.
6. The pharmaceutical composition of any one of claims 1-5, wherein the encoded antigen binding domain comprises (i) a light chain (LC) CDR1, LC CDR2 and LC CDR3 of an anti-CD19 light chain binding domain amino acid sequence with 70-100% sequence identity to SEQ ID NO: 25, SEQ ID NO: 27 and SEQ ID NO: 29, respectively, and/or (ii) a heavy chain (HC) CDR1, HC CDR2 and HC CDR3 of an anti-CD19 heavy chain binding domain amino acid sequence with 70-100% sequence identity to SEQ ID NO: 31, SEQ ID NO: 33 and SEQ ID NO: 35, respectively.

7. The pharmaceutical composition of any one of claims 1-6, wherein the TFP includes an extracellular domain of a TCR subunit that comprises an extracellular domain or portion thereof of a protein selected from the group consisting of a TCR alpha chain, a TCR beta chain, a CD3 epsilon TCR subunit, a CD3 gamma TCR subunit, a CD3 delta TCR subunit, functional fragments thereof, and amino acid sequences thereof having at least one but not more than 20 modifications.