engineered T cells requires the T cells to be capable of strong activation, expansion, persistence over time, effective tumor targeting, reduced and, in case of relapsing disease, to enable a 'memory' response. In addition, CAR therapies currently being developed have been associated with the release of high levels of pro-inflammatory cytokines that have been associated with dose-limiting toxicities.

SUMMARY

[0007] There is a clear need to develop improved genetically engineered T cells to act against various human malignancies, including CD70 expressing malignancies. Described herein are novel fusion proteins of TCR subunits, including CD3 epsilon, CD3gamma and CD3 delta, and of TCR alpha and TCR beta chains with binding domains specific to CD70 that have the potential to overcome limitations of existing approaches.

[0007a] In one aspect, the present disclosure refers to a recombinant nucleic acid molecule comprising a sequence encoding a T cell receptor (TCR) fusion protein (TFP) wherein the TFP comprises:

(a) a TCR subunit comprising:

(i) at least a portion of a TCR extracellular domain, and

(ii) a TCR transmembrane domain,

(iii) a TCR intracellular domain, and

(b) an antigen binding domain that specifically binds CD70; and

wherein the TCR subunit and the antigen binding domain are operatively linked.

[0007b] In another aspect, the present disclosure refers to a recombinant nucleic acid molecule comprising a sequence encoding an antibody or a fragment thereof that specifically binds CD70, wherein the antibody or fragment thereof is the antigen binding domain as described herein.

[0007c] In another aspect, the present disclosure refers to a vector comprising the recombinant nucleic acid molecule as desribed herein.

[0007d] In another aspect, the present disclosure refers to a cell comprising the recombinant nucleic acid molecule as described herein, or the vector as described herein.

[0007e] In another aspect, the present disclosure refers to a T cell comprising a recombinant nucleic acid molecule of any one of claims 1-40, wherein the recombinant nucleic acid molecule comprises a sequence encoding a T cell receptor (TCR) fusion protein (TFP), wherein the TFP comprises:

(a) a TCR subunit comprising:

(i) at least a portion of a TCR extracellular domain, and

(ii) a TCR transmembrane domain,

(iii) a TCR intracellular domain, and

(b) an antigen binding domain that specifically binds CD70; and

wherein the TCR subunit and the antigen binding domain are operatively linked.

[0007f] In another aspect, the present disclosure refers to a pharmaceutical composition comprising the cell or T cell as described herein and a pharmaceutically acceptable carrier for use in therapy.

[0007g] In another aspect, the present disclosure refers to a method of producing the cell or T cell as described herein, the method comprising:

(A) (i) disrupting an endogenous CD70 gene, thereby producing a cell or T cell containing a functional disruption of an endogenous CD70 gene; and

(ii) transducing the cell or T cell containing the functional disruption of the endogenous CD70 gene with the recombinant nucleic acid of any one of claims 1-40, or the vector of claim 41;

(B) (i) disrupting an endogenous CIITA gene, thereby producing a cell or T cell containing a functional disruption of an endogenous CIITA gene; and

(ii) transducing the cell or T cell containing the functional disruption of the endogenous CD70 gene or the functional disruption of the endogenous CIITA gene with the recombinant nucleic acid of any one of claims 1-40, or the vector of claim 41;

(C) (i) transducing a cell or T cell with the recombinant nucleic acid of any one of claims 1-40, or the vector of claim 41; and

(ii) contacting the cell or T cell with an anti-CD70 antibody that binds to CD70 on the cell surface; or

(D) transducing a cell or T cell with the recombinant nucleic acid of any one of claims 1-40, or the vector of claim 41, and a sequence encoding a fusion protein comprising an anti-CD70 antibody domain and an ER retention domain.

[0007h] In another aspect, the present disclosure refers to a use of a pharmaceutical composition comprising the cell or T cell as described herein and a pharmaceutically acceptable carrier, or the pharmaceutical composition as described herein in the manufacture of a medicament for treating cancer in a subject in need thereof, wherein an effective amount of the pharmaceutical composition is administered to the subject, thereby treating the cancer in the subject

[0008] Provided herein are recombinant nucleic acid molecules comprising a sequence encoding a T cell receptor (TCR) fusion protein (TFP) wherein the TFP comprises: (a) a TCR subunit comprising: (i) at least a portion of a TCR extracellular domain, and (ii) a TCR transmembrane domain, (iii) a TCR intracellular domain, and (b) an antigen binding domain that specifically binds CD70; and wherein the TCR subunit and the antigen binding domain are operatively linked.

[0009] In some embodiments, the TFP functionally interacts with an endogenous TCR complex

when expressed in a T cell.

[0010] In some embodiments, the TCR intracellular domain comprises a stimulatory domain from an intracellular signaling domain of CD3 gamma, CD3 delta, or CD3 epsilon.

[0011] In some embodiments, a T cell expressing the TFP exhibits increased cytotoxicity to a human cell expressing CD70 compared to a T cell not containing the TFP.

[0012] In some embodiments, the antigen binding domain is connected to the TCR extracellular domain by a linker sequence.

[0013] In some embodiments, the linker is 120 amino acids in length or less.

[0014] In some embodiments, the linker sequence comprises $(G_4S)_n$, wherein G is glycine, S is serine, and n is an integer from 1 to 10.

[0015] In some embodiments, n is an integer from 1 to 4.

[0016] In some embodiments, at least two of the TCR extracellular domain, the TCR transmembrane domain, and the TCR intracellular domain are from the same TCR subunit.

[0017] In some embodiments, at least two of the TCR extracellular domain, the TCR transmembrane domain, and the TCR intracellular domain are from TCR alpha.

[0018] In some embodiments, at least two of the TCR extracellular domain, the TCR transmembrane domain, and the TCR intracellular domain are from TCR beta.