

MULTIFUNCTIONAL MOLECULES THAT BIND TO T CELL RELATED CANCER CELLS AND USES THEREOF

RELATED APPLICATION

5 This application claims priority to U.S. Serial No. 62/808,646 filed February 21, 2019, the contents of which are incorporated herein by reference in their entireties.

SEQUENCE LISTING

10 The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on February 19, 2020, is named E2070-7022WO_SL.txt and is 810,998 bytes in size.

BACKGROUND

15 Lymphomas are cancers that arise from lymphocytes. T cell lymphoma (TCL) is a lymphoma that arises from T cells; these account for approximately 7% of all non-Hodgkin's lymphomas in the United States. Common subtypes of TCL include: Peripheral T Cell Lymphoma, Not Otherwise Specified (PTCLNOS), Anaplastic Large Cell Lymphoma (ALCL), Angioimmunoblastic T Cell Lymphoma (AITL), and Cutaneous T Cell Lymphoma (CTCL). Each type of TCL has its own pathology and symptoms. Given the ongoing need for improved treatment of lymphomas such as TCLs, new compositions and treatments targeting lymphomas, e.g., TCLs, are highly desirable.

SUMMARY

25 In one aspect, the present disclosure provides a multifunctional molecule, comprising: (1) a first antigen binding domain that selectively binds to T cell receptor beta chain constant domain 1 (TRBC1) or T cell receptor beta chain constant domain 2 (TRBC2), and (2) a second antigen binding domain that selectively binds to NKp30.

In another aspect, the present disclosure provides a polynucleotide comprising a sequence encoding the multifunctional molecule as described herein. In another aspect, the present disclosure provides a host cell comprising the polynucleotide as described herein.

In another aspect, the present disclosure provides a method of making the multifunctional molecule as described herein, comprising culturing the host cell as described herein, under suitable conditions for gene expression and/or homo- or heterodimerization.

5 In another aspect, the present disclosure provides a medicament comprising the multifunctional molecule as described herein, and a pharmaceutically acceptable carrier, excipient, or stabilizer.

10 In another aspect, the present disclosure provides a use of a pharmaceutical composition comprising the multifunctional molecule as described herein in the manufacture of a medicament for treating cancer in a subject in need thereof, ~~optionally~~, wherein the subject has cancer cells that express a T cell receptor comprising TRBC1 or TRBC2.

In yet another aspect, the present disclosure provides a pharmaceutical composition comprising the multifunctional molecule as described herein for use in therapy.

15 The disclosure relates, inter alia, to novel multispecific or multifunctional molecules that include (i) an antigen binding domain that binds to a tumor antigen on a lymphoma cell (e.g., a T cell), e.g., a T cell receptor comprising T cell receptor beta chain constant domain 1 (TRBC1) or a T cell receptor comprising T cell receptor beta chain constant domain 2 (TRBC2); and one, two or all of: (ii) an immune cell engager (e.g., chosen from an NK cell engager, a T cell engager, a B cell engager, a dendritic cell engager, or a macrophage cell engager); (iii) a cytokine molecule;

We claim:

1. A multifunctional molecule, comprising:
 - ~~(1i)~~ a first antigen binding domain that selectively binds to T cell receptor beta chain constant domain 1 (TRBC1) or T cell receptor beta chain constant domain 2 (TRBC2), and
 - ~~(2ii)~~ a second antigen binding domain that selectively binds to NKp30.
2. The multifunctional molecule of claim 1, wherein the first antigen binding domain comprises:
 - (i) a heavy chain variable region (VH) comprising a heavy chain complementarity determining region 1 (VHCDR1), a heavy chain complementarity determining region 2 (VHCDR2), and a heavy chain complementarity determining region 3 (VHCDR3) comprising the sequences of:
 - (a) SEQ ID NO: 200, SEQ ID NO: 201, and SEQ ID NO: 202, respectively;
 - (b) SEQ ID NO: 7346, SEQ ID NO: 201, and SEQ ID NO: 202, respectively;
 - (c) SEQ ID NO: 7354, SEQ ID NO: 201, and SEQ ID NO: 202, respectively;
 - (d) SEQ ID NO: 7346, SEQ ID NO: 7355, and SEQ ID NO: 202, respectively; or
 - (e) SEQ ID NO: 7354, SEQ ID NO: 7355, and SEQ ID NO: 202, respectively; and
 - (ii) a light chain variable region (VL) comprising a light chain complementarity determining region 1 (VLCDR1), a light chain complementarity determining region 2 (VLCDR2), and a light chain complementarity determining region 3 (VLCDR3) comprising the sequences of:
 - (a) SEQ ID NO: 223, SEQ ID NO: 224, and SEQ ID NO: 225, respectively;
 - (b) SEQ ID NO: 7367, SEQ ID NO: 224, and SEQ ID NO: 225, respectively;
 - (c) SEQ ID NO: 223, SEQ ID NO: 7368, and SEQ ID NO: 225, respectively;
 - (d) SEQ ID NO: 223, SEQ ID NO: 224, and SEQ ID NO: 7369, respectively; or
 - (e) SEQ ID NO: 7367, SEQ ID NO: 7368, and SEQ ID NO: 7369, respectively. (a)-a heavy-chain-variable-region-(VH)-comprising
 - (i) a heavy-chain-complementarity-determining-region-1 (VHCDR1)-amino-acid-sequence-of-SEQ-ID-NO: 200,
 - (ii) a VHCDR2-amino-acid-sequence-of-SEQ-ID-NO: 201, and
 - (iii) a VHCDR3-amino-acid-sequence-of-SEQ-ID-NO: 202; and/or

- ~~(b) a light chain variable region (VL) comprising~~
~~(i) a light chain complementarity determining region 1 (VLCDR1) amino acid sequence of SEQ ID NO: 223,~~
~~(ii) a VLCDR2 amino acid sequence of SEQ ID NO: 224, and~~
~~(iii) a VLCDR3 amino acid sequence of SEQ ID NO: 225.~~

3. The multifunctional molecule of claim 1 or 2, wherein
the first antigen binding domain comprises:

- (i) a VH comprising a VHCDR1, a VHCDR2, and a VHCDR3 comprising the sequences of SEQ ID NO: 7346, SEQ ID NO: 7355, and SEQ ID NO: 202, respectively; and a VL comprising a VLCDR1, a VLCDR2, and a VLCDR3 comprising the sequences of SEQ ID NO: 223, SEQ ID NO: 224, and SEQ ID NO: 225, respectively;
(ii) a VH comprising a VHCDR1, a VHCDR2, and a VHCDR3 comprising the sequences of SEQ ID NO: 7346, SEQ ID NO: 7355, and SEQ ID NO: 202, respectively; and a VL comprising a VLCDR1, a VLCDR2, and a VLCDR3 comprising the sequences of SEQ ID NO: 7367, SEQ ID NO: 224, and SEQ ID NO: 225, respectively;
(iii) a VH comprising a VHCDR1, a VHCDR2, and a VHCDR3 comprising the sequences of SEQ ID NO: 7346, SEQ ID NO: 7355, and SEQ ID NO: 202, respectively; and a VL comprising a VLCDR1, a VLCDR2, and a VLCDR3 comprising the sequences of SEQ ID NO: 223, SEQ ID NO: 7368, and SEQ ID NO: 225, respectively;
(iv) a VH comprising a VHCDR1, a VHCDR2, and a VHCDR3 comprising the sequences of SEQ ID NO: 7346, SEQ ID NO: 7355, and SEQ ID NO: 202, respectively; and a VL comprising a VLCDR1, a VLCDR2, and a VLCDR3 comprising the sequences of SEQ ID NO: 223, SEQ ID NO: 224, and SEQ ID NO: 7369, respectively;
(v) a VH comprising a VHCDR1, a VHCDR2, and a VHCDR3 comprising the sequences of SEQ ID NO: 7346, SEQ ID NO: 7355, and SEQ ID NO: 202, respectively; and a VL comprising a VLCDR1, a VLCDR2, and a VLCDR3 comprising the sequences of SEQ ID NO: 7367, SEQ ID NO: 7368, and SEQ ID NO: 7369, respectively;
(vi) a VH comprising a VHCDR1, a VHCDR2, and a VHCDR3 comprising the sequences of SEQ ID NO: 7346, SEQ ID NO: 201, and SEQ ID NO: 202, respectively; and a VL comprising a VLCDR1, a VLCDR2, and a VLCDR3 comprising the sequences of SEQ ID NO: 223, SEQ ID NO: 224, and SEQ ID NO: 225, respectively;

(vii) a VH comprising a VHCDR1, a VHCDR2, and a VHCDR3 comprising the sequences of SEQ ID NO: 7346, SEQ ID NO: 201, and SEQ ID NO: 202, respectively; and a VL comprising a VLCDR1, a VLCDR2, and a VLCDR3 comprising the sequences of SEQ ID NO: 7367, SEQ ID NO: 224, and SEQ ID NO: 225, respectively;

(viii) a VH comprising a VHCDR1, a VHCDR2, and a VHCDR3 comprising the sequences of SEQ ID NO: 7346, SEQ ID NO: 201, and SEQ ID NO: 202, respectively; and a VL comprising a VLCDR1, a VLCDR2, and a VLCDR3 comprising the sequences of SEQ ID NO: 223, SEQ ID NO: 7368, and SEQ ID NO: 225, respectively;

(ix) a VH comprising a VHCDR1, a VHCDR2, and a VHCDR3 comprising the sequences of SEQ ID NO: 7346, SEQ ID NO: 201, and SEQ ID NO: 202, respectively; and a VL comprising a VLCDR1, a VLCDR2, and a VLCDR3 comprising the sequences of SEQ ID NO: 223, SEQ ID NO: 224, and SEQ ID NO: 7369, respectively;

(x) a VH comprising a VHCDR1, a VHCDR2, and a VHCDR3 comprising the sequences of SEQ ID NO: 7346, SEQ ID NO: 201, and SEQ ID NO: 202, respectively; and a VL comprising a VLCDR1, a VLCDR2, and a VLCDR3 comprising the sequences of SEQ ID NO: 7367, SEQ ID NO: 7368, and SEQ ID NO: 7369, respectively;

(xi) a VH comprising a VHCDR1, a VHCDR2, and a VHCDR3 comprising the sequences of SEQ ID NO: 7354, SEQ ID NO: 201, and SEQ ID NO: 202, respectively; and a VL comprising a VLCDR1, a VLCDR2, and a VLCDR3 comprising the sequences of SEQ ID NO: 223, SEQ ID NO: 224, and SEQ ID NO: 225, respectively;

(xii) a VH comprising a VHCDR1, a VHCDR2, and a VHCDR3 comprising the sequences of SEQ ID NO: 7354, SEQ ID NO: 201, and SEQ ID NO: 202, respectively; and a VL comprising a VLCDR1, a VLCDR2, and a VLCDR3 comprising the sequences of SEQ ID NO: 7367, SEQ ID NO: 224, and SEQ ID NO: 225, respectively;

(xiii) a VH comprising a VHCDR1, a VHCDR2, and a VHCDR3 comprising the sequences of SEQ ID NO: 7354, SEQ ID NO: 201, and SEQ ID NO: 202, respectively; and a VL comprising a VLCDR1, a VLCDR2, and a VLCDR3 comprising the sequences of SEQ ID NO: 223, SEQ ID NO: 7368, and SEQ ID NO: 225, respectively;

(xiv) a VH comprising a VHCDR1, a VHCDR2, and a VHCDR3 comprising the sequences of SEQ ID NO: 7354, SEQ ID NO: 201, and SEQ ID NO: 202, respectively;

and a VL comprising a VLCDR1, a VLCDR2, and a VLCDR3 comprising the sequences of SEQ ID NO: 223, SEQ ID NO: 224, and SEQ ID NO: 7369, respectively;

(xv) a VH comprising a VHCDR1, a VHCDR2, and a VHCDR3 comprising the sequences of SEQ ID NO: 7354, SEQ ID NO: 201, and SEQ ID NO: 202, respectively;
and a VL comprising a VLCDR1, a VLCDR2, and a VLCDR3 comprising the sequences of SEQ ID NO: 7367, SEQ ID NO: 7368, and SEQ ID NO: 7369, respectively;

(xvi) a VH comprising a VHCDR1, a VHCDR2, and a VHCDR3 comprising the sequences of SEQ ID NO: 7354, SEQ ID NO: 7355, and SEQ ID NO: 202, respectively;
and a VL comprising a VLCDR1, a VLCDR2, and a VLCDR3 comprising the sequences of SEQ ID NO: 223, SEQ ID NO: 224, and SEQ ID NO: 225, respectively;

(xvii) a VH comprising a VHCDR1, a VHCDR2, and a VHCDR3 comprising the sequences of SEQ ID NO: 7354, SEQ ID NO: 7355, and SEQ ID NO: 202, respectively;
and a VL comprising a VLCDR1, a VLCDR2, and a VLCDR3 comprising the sequences of SEQ ID NO: 7367, SEQ ID NO: 224, and SEQ ID NO: 225, respectively;

(xviii) a VH comprising a VHCDR1, a VHCDR2, and a VHCDR3 comprising the sequences of SEQ ID NO: 7354, SEQ ID NO: 7355, and SEQ ID NO: 202, respectively;
and a VL comprising a VLCDR1, a VLCDR2, and a VLCDR3 comprising the sequences of SEQ ID NO: 223, SEQ ID NO: 7368, and SEQ ID NO: 225, respectively;

(xix) a VH comprising a VHCDR1, a VHCDR2, and a VHCDR3 comprising the sequences of SEQ ID NO: 7354, SEQ ID NO: 7355, and SEQ ID NO: 202, respectively;
and a VL comprising a VLCDR1, a VLCDR2, and a VLCDR3 comprising the sequences of SEQ ID NO: 223, SEQ ID NO: 224, and SEQ ID NO: 7369, respectively;

(xx) a VH comprising a VHCDR1, a VHCDR2, and a VHCDR3 comprising the sequences of SEQ ID NO: 7354, SEQ ID NO: 7355, and SEQ ID NO: 202, respectively;
and a VL comprising a VLCDR1, a VLCDR2, and a VLCDR3 comprising the sequences of SEQ ID NO: 7367, SEQ ID NO: 7368, and SEQ ID NO: 7369, respectively;

(xxi) a VH comprising a VHCDR1, a VHCDR2, and a VHCDR3 comprising the sequences of SEQ ID NO: 200, SEQ ID NO: 201, and SEQ ID NO: 202, respectively;
and a VL comprising a VLCDR1, a VLCDR2, and a VLCDR3 comprising the sequences of SEQ ID NO: 223, SEQ ID NO: 224, and SEQ ID NO: 225, respectively;

(xxii) a VH comprising a VHCDR1, a VHCDR2, and a VHCDR3 comprising the sequences of SEQ ID NO: 200, SEQ ID NO: 201, and SEQ ID NO: 202, respectively; and a VL comprising a VLCDR1, a VLCDR2, and a VLCDR3 comprising the sequences of SEQ ID NO: 7367, SEQ ID NO: 224, and SEQ ID NO: 225, respectively;

(xxiii) a VH comprising a VHCDR1, a VHCDR2, and a VHCDR3 comprising the sequences of SEQ ID NO: 200, SEQ ID NO: 201, and SEQ ID NO: 202, respectively; and a VL comprising a VLCDR1, a VLCDR2, and a VLCDR3 comprising the sequences of SEQ ID NO: 223, SEQ ID NO: 7368, and SEQ ID NO: 225, respectively;

(xxiv) a VH comprising a VHCDR1, a VHCDR2, and a VHCDR3 comprising the sequences of SEQ ID NO: 200, SEQ ID NO: 201, and SEQ ID NO: 202, respectively; and a VL comprising a VLCDR1, a VLCDR2, and a VLCDR3 comprising the sequences of SEQ ID NO: 223, SEQ ID NO: 224, and SEQ ID NO: 7369, respectively; or

(xxv) a VH comprising a VHCDR1, a VHCDR2, and a VHCDR3 comprising the sequences of SEQ ID NO: 200, SEQ ID NO: 201, and SEQ ID NO: 202, respectively; and a VL comprising a VLCDR1, a VLCDR2, and a VLCDR3 comprising the sequences of SEQ ID NO: 7367, SEQ ID NO: 7368, and SEQ ID NO: 7369, respectively.

~~(a) the VH comprises:~~

~~(i) a heavy chain framework region 1 (VHFWR1) amino acid sequence with at least 90% sequence identity to SEQ ID NO: 203;~~

~~(ii) a VHFWR2 amino acid sequence with at least 90% sequence identity to SEQ ID NO: 204;~~

~~(iii) a VHFWR3 amino acid sequence with at least 90% sequence identity to SEQ ID NO: 205; and~~

~~(iv) a VHFWR4 amino acid sequence with at least 90% sequence identity to SEQ ID NO: 206; and/or~~

~~(b) the VL comprises~~

~~(i) a light chain framework region 1 (VLFWR1) amino acid sequence with at least 90% sequence identity to SEQ ID NO: 226;~~

~~(ii) a VLFWR2 amino acid sequence with at least 90% sequence identity to SEQ ID NO: 227;~~

~~(iii) a VLFWR2 amino acid sequence with at least 90% sequence identity to SEQ ID NO: 228, and~~

~~(iv) a VLFWR2 amino acid sequence with at least 90% sequence identity to SEQ ID NO: 229.~~

4. The multifunctional molecule of ~~any one of claims 2 or 1-3~~, wherein the first antigen binding domain comprises:

(i) a VH comprising an amino acid sequence with at least 85% sequence identity to any one selected from the group consisting of SEQ ID NOs: 250-254, 7343, 7344, and 7350-7352,

optionally, wherein the VH comprises any one amino acid sequence selected from the group consisting of SEQ ID NOs: 250-254, 7343, 7344, and 7350-7352; and/or

(ii) a VL comprising an amino acid sequence with at least 85% sequence identity to any one selected from the group consisting of SEQ ID NOs: 255-260, and 7357-7360,

optionally, wherein the VL comprises any one amino acid sequence selected from the group consisting of SEQ ID NOs: 255-260, and 7357-7360.

~~(a) the VH comprises:~~

~~(i) a heavy chain framework region 1 (VHFWR1) amino acid sequence with at least 90% sequence identity to SEQ ID NO: 215,~~

~~(ii) a VHFWR2 amino acid sequence with at least 90% sequence identity to SEQ ID NO: 216,~~

~~(iii) a VHFWR3 amino acid sequence with at least 90% sequence identity to SEQ ID NO: 217, and~~

~~(iv) a VHFWR4 amino acid sequence with at least 90% sequence identity to SEQ ID NO: 218; and/or~~

~~(b) the VL comprises~~

~~(i) a light chain framework region 1 (VLFWR1) amino acid sequence with at least 90% sequence identity to SEQ ID NO: 238,~~

~~(ii) a VLFWR2 amino acid sequence with at least 90% sequence identity to SEQ ID NO: 239,~~

~~(iii) a VLFWR2 amino acid sequence with at least 90% sequence identity to SEQ ID NO: 240, and~~

- ~~(iv) a VLFWR2 amino acid sequence with at least 90% sequence identity to SEQ ID NO: 241.~~
5. The multifunctional molecule of any one of claims ~~21~~-4, wherein the first antigen binding domain comprises:
- (i) a VH comprising an amino acid sequence with at least 85% sequence identity to the sequence of SEQ ID NO: 7351 and a VL comprising an amino acid sequence with at least 85% sequence identity to the sequence of SEQ ID NO: 258,
optionally, wherein the VH comprises the sequence of SEQ ID NO: 7351 and the VL comprises the sequence of SEQ ID NO: 258; and/or
 - (ii) a VH comprising an amino acid sequence with at least 85% sequence identity to the sequence of SEQ ID NO: 253 and a VL comprising an amino acid sequence with at least 85% sequence identity to the sequence of SEQ ID NO: 258,
optionally, wherein the VH comprises the sequence of SEQ ID NO: 253 and the VL comprises the sequence of SEQ ID NO: 258.
 - ~~(a) the VH comprises an amino acid sequence with at least 75% sequence identity to SEQ ID NO: 250; and~~
 - ~~(b) the VL comprises an amino acid sequence with at least 75% sequence identity to SEQ ID NO: 255.~~
6. The multifunctional molecule of any one of claims ~~21~~-5, wherein the first antigen binding domain comprises:
- (i) a heavy chain comprising an amino acid sequence with at least 75% sequence identity to any one selected from the group consisting of SEQ ID NOs: 6154, 6155, 6167, 6168, and 6191,
optionally, wherein the heavy chain comprises any one amino acid selected from the group consisting of SEQ ID NOs: 6154, 6155, 6167, 6168, and 6191; and/or
 - (ii) a light chain comprising an amino acid sequence with at least 75% sequence identity to any one selected from the group consisting of SEQ ID NOs: 6156 and 6169,
optionally, wherein the light chain comprises any one amino acid selected from the group consisting of SEQ ID NOs: 6156 and 6169.
- ~~the first antigen binding domain has a higher affinity for a T cell receptor comprising TRBC1 than for a T cell receptor comprising TRBC2.~~

7. The multifunctional molecule of any one of claims 1-6, wherein the second antigen binding domain comprises:

(i) a VH comprising a VHCDR1, a VHCDR2, and a VHCDR3 comprising the sequences of:

(a) SEQ ID NO: 6000, SEQ ID NO: 6001, and SEQ ID NO: 6002, respectively;

(b) SEQ ID NO: 7313, SEQ ID NO: 6001, and SEQ ID NO: 6002, respectively;

(c) SEQ ID NO: 6007, SEQ ID NO: 6008, and SEQ ID NO: 6009, respectively;

(d) SEQ ID NO: 7313, SEQ ID NO: 6008, and SEQ ID NO: 6009, respectively;

(e) SEQ ID NO: 7313, SEQ ID NO: 7385, and SEQ ID NO: 7315, respectively;

(f) SEQ ID NO: 7313, SEQ ID NO: 7318, and SEQ ID NO: 6009, respectively; or

(g) SEQ ID NO: 7313, SEQ ID NO: 6001, and SEQ ID NO: 7315, respectively; and

(ii) a VL comprising a VLCDR1, a VLCDR2, and a VLCDR3 comprising the sequences of:

(a) SEQ ID NO: 6063, SEQ ID NO: 6064, and SEQ ID NO: 7293, respectively;

(b) SEQ ID NO: 6070, SEQ ID NO: 6071, and SEQ ID NO: 6072, respectively;

(c) SEQ ID NO: 6070, SEQ ID NO: 6064, and SEQ ID NO: 7321, respectively; or

(d) SEQ ID NO: 7326, SEQ ID NO: 7327, and SEQ ID NO: 7329, respectively;

~~(a) a heavy chain variable region (VH) comprising~~

~~(i) a heavy chain complementarity determining region 1 (VHCDR1) amino acid sequence of SEQ ID NO: 6000,~~

~~(ii) a VHCDR2 amino acid sequence of SEQ ID NO: 6001, and~~

~~(iii) a VHCDR3 amino acid sequence of SEQ ID NO: 6002; and/or~~

~~(b) a light chain variable region (VL) comprising~~

~~(i) a light chain complementarity determining region 1 (VLCDR1) amino acid sequence of SEQ ID NO: 6063,~~

~~(ii) a VLCDR2 amino acid sequence of SEQ ID NO: 6064, and~~

~~(iii) a VLCDR3 amino acid sequence of SEQ ID NO: 7293.~~

8. The multifunctional molecule of any one of claim 1-7, wherein the second antigen binding domain comprises:

(i) a VH comprising a VHCDR1, a VHCDR2, and a VHCDR3 comprising the sequences of SEQ ID NO: 6000, SEQ ID NO: 6001, and SEQ ID NO: 6002, respectively, or SEQ

ID NO: 7313, SEQ ID NO: 6001, and SEQ ID NO: 6002, respectively; and a VL comprising a VLCDR1, a VLCDR2, and a VLCDR3 comprising the sequences of SEQ ID NO: 6063, SEQ ID NO: 6064, and SEQ ID NO: 7293, respectively;

(ii) a VH comprising a VHCDR1, a VHCDR2, and a VHCDR3 comprising the sequences of SEQ ID NO: 6007, SEQ ID NO: 6008, and SEQ ID NO: 6009, respectively, or SEQ ID NO: 7313, SEQ ID NO: 6008, and SEQ ID NO: 6009, respectively; and a VL comprising a VLCDR1, a VLCDR2, and a VLCDR3 comprising the sequences of SEQ ID NO: 6070, SEQ ID NO: 6071, and SEQ ID NO: 6072, respectively;

(iii) a VH comprising a VHCDR1, a VHCDR2, and a VHCDR3 comprising the sequences of SEQ ID NO: 7313, SEQ ID NO: 7385, and SEQ ID NO: 7315, respectively; and a VL comprising a VLCDR1, a VLCDR2, and a VLCDR3 comprising the sequences of SEQ ID NO: 6070, SEQ ID NO: 6064, and SEQ ID NO: 7321, respectively;

(iv) a VH comprising a VHCDR1, a VHCDR2, and a VHCDR3 comprising the sequences of SEQ ID NO: 7313, SEQ ID NO: 7318, and SEQ ID NO: 6009, respectively; and a VL comprising a VLCDR1, a VLCDR2, and a VLCDR3 comprising the sequences of SEQ ID NO: 6070, SEQ ID NO: 6064, and SEQ ID NO: 7321, respectively; or

(v) a VH comprising a VHCDR1, a VHCDR2, and a VHCDR3 comprising the sequences of SEQ ID NO: 7313, SEQ ID NO: 6001, and SEQ ID NO: 7315, respectively; and a VL comprising a VLCDR1, a VLCDR2, and a VLCDR3 comprising the sequences of SEQ ID NO: 6070, SEQ ID NO: 6071, and SEQ ID NO: 6072, respectively, or SEQ ID NO: 7326, SEQ ID NO: 7327, and SEQ ID NO: 7329, respectively;

~~(a) a VH comprises:~~

~~(i) a heavy chain framework region 1 (VHFWR1) amino acid sequence with at least 90% sequence identity to SEQ ID NO: 6003,~~

~~(ii) a VHFWR2 amino acid sequence with at least 90% sequence identity to SEQ ID NO: 6004,~~

~~(iii) a VHFWR3 amino acid sequence with at least 90% sequence identity to SEQ ID NO: 6005, and~~

~~(iv) a VHFWR4 amino acid sequence with at least 90% sequence identity to SEQ ID NO: 6006; and/or~~

~~(b) a VL comprises~~

- ~~(i) a light chain framework region 1 (VLFWR1) amino acid sequence with at least 90% sequence identity to SEQ ID NO: 6066;~~
- ~~(ii) a VLFWR2 amino acid sequence with at least 90% sequence identity to SEQ ID NO: 6067;~~
- ~~(iii) a VLFWR2 amino acid sequence with at least 90% sequence identity to SEQ ID NO: 7292; and~~
- ~~(iv) a VLFWR2 amino acid sequence with at least 90% sequence identity to SEQ ID NO: 6069.~~

9. The multifunctional molecule of any one of claim 7 or 8, wherein the second antigen binding domain comprises:

- (i) a VH comprising an amino acid sequence with at least 85% sequence identity to any one selected from the group consisting of SEQ ID NOs: 6121-6134, 7295, 7297, 7298, and 7300-7304,
optionally, wherein the VH comprises any one amino acid sequence selected from the group consisting of SEQ ID NOs: 6121-6134, 7295, 7297, 7298, and 7300-7304;
and/or
- (ii) a VL comprising an amino acid sequence with at least 85% sequence identity to any one selected from the group consisting of SEQ ID NOs: 6136-6147, 7294, 7296, 7299, and 7305-7309,
optionally, wherein the VL comprises any one amino acid sequence selected from the group consisting of SEQ ID NOs: 6136-6147, 7294, 7296, 7299, and 7305-7309(a) a VH comprises an amino acid sequence with at least 75% sequence identity to SEQ ID NO: 250 or 6121; and
(b) a VL comprises an amino acid sequence with at least 75% sequence identity to SEQ ID NO: 255 or 7294.

10. The multifunctional molecule of any one of claims 71-9, wherein the second antigen binding domain comprises:

- (i) a VH comprising an amino acid sequence with at least 85% sequence identity to any one selected from the group consisting of SEQ ID NOs: 6121 and 6123-6128; and a VL comprising an amino acid sequence with at least 85% sequence identity to any one selected from the group consisting of SEQ ID NOs: 7294 and 6137-6141,

optionally, wherein the VH comprises any one amino acid sequence selected from the group consisting of SEQ ID NOs: 6121 and 6123-6128; and the VL comprises any one amino acid sequence selected from the group consisting of SEQ ID NOs: 7294 and 6137-6141;

(ii) a VH comprising an amino acid sequence with at least 85% sequence identity to any one selected from the group consisting of SEQ ID NOs: 6122 and 6129-6134; and a VL comprising an amino acid sequence with at least 85% sequence identity to any one selected from the group consisting of SEQ ID NOs: 6136 and 6142-6147;

optionally, wherein the VH comprises any one amino acid sequence selected from the group consisting of SEQ ID NOs: 6122 and 6129-6134; and the VL comprises any one amino acid sequence selected from the group consisting of SEQ ID NOs: 6136 and 6142-6147;

(iii) a VH comprising an amino acid sequence with at least 85% sequence identity to the sequence of SEQ ID NO: 7295 or the sequence of SEQ ID NO: 7297; and a VL comprising an amino acid sequence with at least 85% sequence identity to the sequence of SEQ ID NO: 7296;

optionally, wherein the VH comprises the sequence of SEQ ID NO: 7295 or the sequence of SEQ ID NO: 7297; and the VL comprises the sequence of SEQ ID NO: 7296;

(iv) a VH comprising an amino acid sequence with at least 85% sequence identity to the sequence of SEQ ID NO: 6122; and a VL comprising an amino acid sequence with at least 85% sequence identity to the sequence of SEQ ID NO: 6136; or

optionally, wherein the VH comprises the sequence of SEQ ID NO: 6122; and the VL comprises the sequence of SEQ ID NO: 6136; or

(v) a VH comprising an amino acid sequence with at least 85% sequence identity to any one selected from the group consisting of SEQ ID NOs: 7298 and 7300-7304; and a VL comprising an amino acid sequence with at least 85% sequence identity to any one selected from the group consisting of SEQ ID NOs: 7299 and 7305-7309,

optionally, wherein the VH comprises any one amino acid sequence selected from the group consisting of SEQ ID NOs: 7298 and 7300-7304; and the VL comprises any

one amino acid sequence selected from the group consisting of SEQ ID NOs: 7299 and 7305-7309~~the multifunctional molecule further comprises a cytokine molecule.~~

11. The multifunctional molecule of any one of claims 7-10, wherein the second antigen binding domain comprises a VH comprising an amino acid sequence with at least 85% sequence identity to the sequence of SEQ ID NO: 7302, and a VL comprising an amino acid sequence with at least 85% sequence identity to the sequence of SEQ ID NO: 7309 or the sequence of SEQ ID NO: 7305,

optionally, wherein the VH comprises the sequence of SEQ ID NO: 7302, and the VL comprises the sequence of SEQ ID NO: 7309 or the sequence of SEQ ID NO: 7305~~the cytokine molecule is interleukin 2 (IL-2), interleukin 7 (IL-7), interleukin 12 (IL-12), interleukin 15 (IL-15), interleukin 18 (IL-18), interleukin 21 (IL-21), or interferon gamma.~~

12. The multifunctional molecule of any one of claims ~~7~~4-11, wherein the second antigen binding domain comprises:

(i) a heavy chain comprising an amino acid sequence with at least 80% sequence identity to any one selected from the group consisting of SEQ ID NOs: 6148, 6149, 6151, and 6152,

optionally, wherein the heavy chain comprises any one amino acid sequence selected from the group consisting of SEQ ID NOs: 6148, 6149, 6151, and 6152; and/or

(ii) a light chain comprising an amino acid sequence with at least 80% sequence identity to the sequence of SEQ ID NO: 6150 or the sequence of SEQ ID NO: 6153,

optionally, wherein the light chain comprises the amino acid sequence of SEQ ID NO: 6150 or the amino acid sequence of SEQ ID NO: 6153~~the multifunctional molecule further comprises a TGF beta inhibitor.~~

13. The multifunctional molecule of any one of claims 7-12, wherein the second antigen binding domain comprises:

(i) a heavy chain comprising an amino acid sequence with at least 80% sequence identity to the sequence of SEQ ID NO: 6148 or the sequence of SEQ ID NO: 6149; and a light chain comprising an amino acid sequence with at least 80% sequence identity to the sequence of SEQ ID NO: 6150,

optionally, wherein the heavy chain comprises the sequence of SEQ ID NO: 6148 or the sequence of SEQ ID NO: 6149; and the light chain comprises the sequence of SEQ ID NO: 6150;

(ii) a heavy chain comprising an amino acid sequence with at least 80% sequence identity to the sequence of SEQ ID NO: 6151 or the sequence of SEQ ID NO: 6152; and a light chain comprising an amino acid sequence with at least 80% sequence identity to the sequence of SEQ ID NO: 6153,

optionally, wherein the heavy chain comprises the sequence of SEQ ID NO: 6151 or the sequence of SEQ ID NO: 6152; and the light chain comprises to the sequence of SEQ ID NO: 6153; or

(iii) an amino acid sequence with at least 85% sequence identity to any one selected from the group consisting of SEQ ID NOs: 6187- 6190, 7310, and 7311,

optionally, wherein the amino acid sequence is selected from the group consisting of SEQ ID NOs: 6187- 6190, 7310, and 7311~~the TGF-beta inhibitor comprises a portion of a TGF-beta receptor.~~

14. The multifunctional molecule of any one of claims 1-13, wherein the first antigen binding domain comprises an Fab or an scFv, and/or the second antigen binding domain comprises an Fab or an scFv.

~~(a) the first antigen binding domain comprises the VH and VL as recited in claim 2,~~

~~(b) the second antigen binding domain comprises the VH and VL as recited in claim 10,~~
~~and~~

~~(c) the multifunctional molecule further comprises a cytokine molecule that is IL-2.~~

15. The multifunctional molecule of any one of claims 1-14, wherein the multifunctional molecule comprises: -an immunoglobulin constant domain.

(i) the first antigen binding domain comprising the sequence of SEQ ID NO: 7351 and the sequence of SEQ ID NO: 258, and the second antigen binding domain comprising the sequence of SEQ ID NO: 7302 and the sequence of SEQ ID NO: 7309;

(ii) the first antigen binding domain comprising the sequence of SEQ ID NO: 7351 and the sequence of SEQ ID NO: 258, and the second antigen binding domain comprising the sequence of SEQ ID NO: 7311;

(iii) the first antigen binding domain comprising the sequence of SEQ ID NO: 253 and the sequence of SEQ ID NO: 258, and the second antigen binding domain comprising the sequence of SEQ ID NO: 7302 and the sequence of SEQ ID NO: 7309;

(iv) the first antigen binding domain comprising the sequence of SEQ ID NO: 253 and the sequence of SEQ ID NO: 258, and the second antigen binding domain comprising the sequence of SEQ ID NO: 7311;

(v) the first antigen binding domain comprising the sequence of SEQ ID NO: 7351 and the sequence of SEQ ID NO: 258, and the second antigen binding domain comprising the sequence of SEQ ID NO: 7302 and the sequence of SEQ ID NO: 7305;

(vi) the first antigen binding domain comprising the sequence of SEQ ID NO: 7351 and the sequence of SEQ ID NO: 258, and the second antigen binding domain comprising the sequence of SEQ ID NO: 7310;

(vii) the first antigen binding domain comprising the sequence of SEQ ID NO: 253 and the sequence of SEQ ID NO: 258, and the second antigen binding domain comprising the sequence of SEQ ID NO: 7302 and the sequence of SEQ ID NO: 7305; or

(viii) the first antigen binding domain comprising the sequence of SEQ ID NO: 253 and the sequence of SEQ ID NO: 258, and the second antigen binding domain comprising the sequence of SEQ ID NO: 7310.

16. The multifunctional molecule of any one of claims 1-~~claim~~15, wherein the multifunctional molecule comprises: immunoglobulin-constant domain-mediates antibody dependent cellular cytotoxicity, or mediates complement dependent cytotoxicity.

(i) the first antigen binding domain comprising the sequence of SEQ ID NO: 7379 and the sequence of SEQ ID NO: 7380, and the second antigen binding domain comprising the sequence of SEQ ID NO: 7381;

(ii) the first antigen binding domain comprising the sequence of SEQ ID NO: 7382 and the sequence of SEQ ID NO: 7380, and the second antigen binding domain comprising the sequence of SEQ ID NO: 7383;

(iii) the first antigen binding domain comprising the sequence of SEQ ID NO: 7379 and the sequence of SEQ ID NO: 7380, and the second antigen binding domain comprising the sequence of SEQ ID NO: 7383;

(iv) the first antigen binding domain comprising the sequence of SEQ ID NO: 7382 and the sequence of SEQ ID NO: 7380, and the second antigen binding domain comprising the sequence of SEQ ID NO: 7384; or

(v) the first antigen binding domain comprising the sequence of SEQ ID NO: 7379 and the sequence of SEQ ID NO: 7380, and the second antigen binding domain comprising the sequence of SEQ ID NO: 7384.

17. The multifunctional molecule of any one of claims 1-16, wherein the multifunctional molecule ~~furthercomprises the following configuration:~~

~~A, B [dimerization module] C, D,~~

~~wherein:~~

~~(a) the dimerization module comprises a cytokine molecule, an immunoglobulin constant domain; and~~

~~(b) at least one of A, B, C and D is the first antigen binding domain;~~

~~(c) at least one of A, B, C and D is the second antigen binding domain; and~~

~~(d) at least one of A, B, C and D is the cytokine molecule that is IL-2;~~

~~wherein one of A, B, C and D is optionally absent.~~

18. The multifunctional molecule of claim 17, wherein the cytokine molecule is interleukin-2 (IL-2) or functional variant thereof, interleukin-7 (IL-7) or functional variant thereof, interleukin-12 (IL-12) or functional variant thereof, interleukin-15 (IL-15) or functional variant thereof, interleukin-18 (IL-18) or functional variant thereof, interleukin-21 (IL-21) or functional variant thereof, interferon gamma or functional variant thereof, or any combination thereof.

19. The multifunctional molecule of any one of claims 1-18, wherein the multifunctional molecule comprises a first immunoglobulin chain constant region and a second immunoglobulin chain constant region;

wherein the first antigen binding domain is linked to the first immunoglobulin chain constant region, and the second antigen binding domain is linked to the first immunoglobulin chain constant region or the second immunoglobulin chain constant region;

wherein the first immunoglobulin chain constant region and/or the second immunoglobulin chain constant region comprise:

(i) one or more of a paired cavity-protuberance, an electrostatic interaction, or a strand-exchange; and/or

(ii) one or more mutations that result in reduced or ablated affinity for at least one Fc receptor.

2018. A polynucleotide comprising a sequence encoding the multifunctional molecule of any one of claims 1-1947.

2149. A host cell comprising the polynucleotide of claim 2018.

2220. A method of making the multifunctional molecule of any one of claims 1-1947, comprising culturing the host cell of claim 2149, under suitable conditions for gene expression and/or homo- or heterodimerization.

2324. A medicament comprising the multifunctional molecule of any one of claims 1-1947, and a pharmaceutically acceptable carrier, excipient, or stabilizer.

2422. Use of a pharmaceutical composition comprising the multifunctional molecule of any one of claims 1-1947 in the manufacture of a medicament for treating cancer in a subject in need thereof,

~~optionally~~, wherein the subject has cancer cells that express a T cell receptor comprising TRBC1 or TRBC2.

2523. The use of claim 2422, wherein the cancer is leukemia or lymphoma.

2624. The use of claim 2422 or 2523, wherein the cancer is selected from the group consisting of Acquired immune deficiency syndrome (AIDS)-associated lymphoma, Angioimmunoblastic T-cell lymphoma, Adult T-cell leukemia/lymphoma, Burkitt lymphoma, Central nervous system (CNS) lymphoma, Diffuse large B-cell lymphoma (DLBCL), Lymphoblastic lymphoma, Mantle cell lymphoma (MCL), Peripheral T-cell lymphoma (PTCL), Transformed follicular and transformed mucosa-associated lymphoid tissue (MALT) lymphomas, Cutaneous T-cell lymphoma (mycosis fungoides and Sezary syndrome), Follicular lymphoma, Lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia, Marginal zone B-cell lymphoma, Gastric mucosa-associated lymphoid tissue (MALT) lymphoma, Chronic lymphocytic leukemia/small-cell lymphocytic lymphoma (CLL/SLL), Extranodal T-/NK-cell lymphoma (nasal type), and Anaplastic large-cell lymphoma.

~~2725~~. The use of claim ~~264~~,

wherein the cancer is Peripheral T-cell lymphoma (PTCL), and the PTCL is Hepatosplenic T-cell lymphoma (HSGDTCL), Subcutaneous panniculitis-like T-cell lymphoma, or Enteropathy-associated T-cell lymphoma; or

wherein the cancer is Anaplastic large-cell lymphoma, and the Anaplastic large-cell lymphoma is primary cutaneous anaplastic large-cell lymphoma or systemic anaplastic large-cell lymphoma.

~~2826~~. A pharmaceutical composition comprising the multifunctional molecule of any one of claims 1-~~1917~~ for use in therapy.