

CLAIMS

WHAT IS CLAIMED IS:

1. ~~A method of identifying a subject in need of treatment for cancer using a composition, the method comprising:~~
 - ~~1. determining, based at least in part on an assay of a sample from a polypeptide molecule subject, whether the subject has cancer cells that express T cell receptor comprising:~~
 - ~~(a) (i) a first antigen binding domain that binds to~~ T cell receptor beta chain constant domain 1 (TRBC1) or T cell receptor beta chain constant domain 2 (TRBC2);~~); and~~
 - ~~(ii) a second antigen binding domain that binds to NKp30,~~
~~comprising determining whether a subject has cancer cells that express a T cell receptor comprising TRBC2, wherein:~~
 - ~~(b) identifying the subject as a candidate for the treatment based at least in part on the determination that the subject has cancer cells that express a T cell receptor comprising TRBC2 identifies the subject as a candidate for treatment using a multifunctional molecule comprising an antigen binding domain that binds to TRBC2, and optionally identifies the subject as not being as a candidate for TRBC1 or identifying the subject as a candidate for the treatment using a multifunctional molecule comprising an antigen binding domain that binds to TRBC1, based at least in part on the determination that the subject has cancer cells that TRBC2,~~
2. ~~The method of claim 1, wherein the treatment uses a composition comprising a polypeptide molecule is a multifunctional polypeptide molecule that comprises:~~
3. ~~The method of claim 1 or 2, wherein the polypeptide molecule is a multispecific polypeptide molecule. The method of any one of claims 1-3, wherein the~~ (i) a first antigen binding domain that binds to T cell receptor beta chain constant domain 2 (TRBC1 or TRBC2), and ~~the~~ (ii) a second antigen binding domain that binds to NKp30.
- 4.2. The method of 1, wherein the polypeptide molecule comprises a first antigen binding domain comprises one or more CDRs, framework regions, variable regions, or antigen binding domains disclosed in any of Tables 21-25, or a sequence having at least 85%, 90%, 95%, or 99% identity thereto that binds to TRBC1 when the subject has been identified to have cancer cells that express TRBC1.

~~3. The method of any one of claims 1-4,~~ The method of 1, wherein the polypeptide molecule comprises a first antigen binding domain that binds to TRBC2 when the subject has been identified to have cancer cells that express TRBC2.

~~5.4. The method of claim 1,~~ wherein the first antigen binding domain binds to ~~T-cell receptor beta chain constant domain 2~~ (TRBC2), and the first antigen binding domain comprises a VH comprising a heavy chain complementarity determining region 1 (VHCDR1), a VHCDR2, and a VHCDR3, and a VL comprising a light chain complementarity determining region 1 (VLCDR1), a VLCDR2, and a VLCDR3, wherein:

the VHCDR1, VHCDR2, and VHCDR3 comprise the amino acid sequences of ~~SEQ ID NOs: 7441, 201, and 7442,~~ GX1X2MH, wherein X1 is Y or F, and X2 is P, H, V, Y, K, or A (SEQ ID NO: 7441), FINPYNDDIQSNERFRG (SEQ ID NO: 201), and GNGX1X2X3DGAYRFFDF, wherein X1 is K or M, X2 is W or N, and X3 is G or F (SEQ ID NO: 7442), respectively; or

the VLCDR1, VLCDR2, and VLCDR3 comprise the amino acid sequences of RSSQNLVHSNGRITYLX, wherein X is Q or H (SEQ ID ~~NOs~~NO: 7443~~;~~), RVSNRFP (SEQ ID NO: 224~~;~~), and SQSTHVPYT (SEQ ID NO: 225~~;~~), respectively.

~~6.5.~~ The method of claim ~~5,4,~~ wherein the VHCDR1, VHCDR2, and VHCDR3 comprise the amino acid sequences of:

SEQ ID NOs: 7422, 201, and 7403, respectively;

SEQ ID NOs: 7401, 201, and 7403, respectively;

SEQ ID NOs: 7394, 201, and 7396, respectively;

SEQ ID NOs: 7346, 201, and 7398, respectively;

SEQ ID NOs: 7346, 201, and 7400, respectively;

SEQ ID NOs: 7405, 201, and 7403, respectively;

SEQ ID NOs: 7407, 201, and 7403, respectively;

SEQ ID NOs: 7427, 201, and 7403, respectively; or

SEQ ID NOs: 7430, 201, and 7403, respectively~~;~~, and/or

~~7. The method of claim 5 or 6,~~ wherein the VLCDR1, VLCDR2, and VLCDR3 comprise the amino acid sequences of:

SEQ ID NOs: 7410, 224, and 225, respectively; or

SEQ ID NOs: 7409, 224, and 225, respectively.

~~8.6. The method of any one of claims 5-7,~~ The method of claim 5, wherein the VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, and VLCDR3 comprise the amino acid sequences of:

SEQ ID NOs: 7422, 201, 7403, 7410, 224, and 225, respectively;

SEQ ID NOs: 7401, 201, 7403, 7410, 224, and 225, respectively;
 SEQ ID NOs: 7394, 201, 7396, 7410, 224, and 225, respectively;
 SEQ ID NOs: 7346, 201, 7398, 7410, 224, and 225, respectively;
 SEQ ID NOs: 7346, 201, 7400, 7410, 224, and 225, respectively;
 SEQ ID NOs: 7405, 201, 7403, 7410, 224, and 225, respectively;
 SEQ ID NOs: 7407, 201, 7403, 7410, 224, and 225, respectively;
 SEQ ID NOs: 7427, 201, 7403, 7410, 224, and 225, respectively;
 SEQ ID NOs: 7430, 201, 7403, 7410, 224, and 225, respectively;
 SEQ ID NOs: 7422, 201, 7403, 7409, 224, and 225, respectively;
 SEQ ID NOs: 7401, 201, 7403, 7409, 224, and 225, respectively;
 SEQ ID NOs: 7394, 201, 7396, 7409, 224, and 225, respectively;
 SEQ ID NOs: 7346, 201, 7398, 7409, 224, and 225, respectively;
 SEQ ID NOs: 7346, 201, 7400, 7409, 224, and 225, respectively;
 SEQ ID NOs: 7405, 201, 7403, 7409, 224, and 225, respectively;
 SEQ ID NOs: 7407, 201, 7403, 7409, 224, and 225, respectively;
 SEQ ID NOs: 7427, 201, 7403, 7409, 224, and 225, respectively; or
 SEQ ID NOs: 7430, 201, 7403, 7409, 224, and 225, respectively.

7. The method of any one of claims ~~5-8~~, 4-6, wherein:-

~~9.~~(i) the VH comprises an amino acid sequence having at least 85% identity to any one sequence selected from the group consisting of SEQ ID NOs: 7420, 7423, 7411, 7412, 7413, 7414, 7415, 7416, 7417, 7425, 7428, and 7431 ~~(or a sequence having at least 85%, 90%, 95%, or 99% identity thereto) and/or the VL comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 7419 and 7418 (or a sequence having at least 85%, 90%, 95%, or 99% identity thereto);~~

~~The method of~~ optionally, wherein the VH comprises any one amino acid sequence selected from the group consisting of SEQ ID NOs: 7420, 7423, 7411, 7412, 7413, 7414, 7415, 7416, 7417, 7425, 7428, and 7431; and/or

(ii) the VL comprises an amino acid sequence having at least 85% identity to any one sequence selected from the group consisting of ~~claims 5-9~~, SEQ ID NOs: 7419 and 7418;

optionally, wherein the VL comprises any one amino acid sequence selected from the group consisting of SEQ ID NOs: 7419 and 7418 .

10.8. The method of any one of claims 4-7, wherein the VH and VL comprise ~~the~~-amino acid sequences of having at least 85% sequence identity to:

SEQ ID NOs: 7420 and 7419, respectively ~~(or a sequence having at least 85%, 90%, 95%, or 99% identity thereto);~~₁

SEQ ID NOs: 7423 and 7419, respectively ~~(or a sequence having at least 85%, 90%, 95%, or 99% identity thereto);~~₁

SEQ ID NOs: 7411 and 7419, respectively ~~(or a sequence having at least 85%, 90%, 95%, or 99% identity thereto);~~₁

SEQ ID NOs: 7412 and 7419, respectively ~~(or a sequence having at least 85%, 90%, 95%, or 99% identity thereto);~~₁

SEQ ID NOs: 7413 and 7419, respectively ~~(or a sequence having at least 85%, 90%, 95%, or 99% identity thereto);~~₁

SEQ ID NOs: 7414 and 7419, respectively ~~(or a sequence having at least 85%, 90%, 95%, or 99% identity thereto);~~₁

SEQ ID NOs: 7415 and 7419, respectively ~~(or a sequence having at least 85%, 90%, 95%, or 99% identity thereto);~~₁

SEQ ID NOs: 7416 and 7419, respectively ~~(or a sequence having at least 85%, 90%, 95%, or 99% identity thereto);~~₁

SEQ ID NOs: 7417 and 7419, respectively ~~(or a sequence having at least 85%, 90%, 95%, or 99% identity thereto);~~₁

SEQ ID NOs: 7425 and 7419, respectively ~~(or a sequence having at least 85%, 90%, 95%, or 99% identity thereto);~~₁

SEQ ID NOs: 7428 and 7419, respectively ~~(or a sequence having at least 85%, 90%, 95%, or 99% identity thereto);~~₁

SEQ ID NOs: 7431 and 7419, respectively ~~(or a sequence having at least 85%, 90%, 95%, or 99% identity thereto);~~₁

SEQ ID NOs: 7420 and 7418, respectively ~~(or a sequence having at least 85%, 90%, 95%, or 99% identity thereto);~~₁

SEQ ID NOs: 7423 and 7418, respectively ~~(or a sequence having at least 85%, 90%, 95%, or 99% identity thereto);~~₁

SEQ ID NOs: 7411 and 7418, respectively ~~(or a sequence having at least 85%, 90%, 95%, or 99% identity thereto);~~₁

SEQ ID NOs: 7412 and 7418, respectively ~~(or a sequence having at least 85%, 90%, 95%, or 99% identity thereto);~~₁

SEQ ID NOs: 7413 and 7418, respectively ~~(or a sequence having at least 85%, 90%, 95%, or 99% identity thereto);~~₁

SEQ ID NOs: 7414 and 7418, respectively ~~(or a sequence having at least 85%, 90%, 95%, or 99% identity thereto);~~₁

SEQ ID NOs: 7415 and 7418, respectively ~~(or a sequence having at least 85%, 90%, 95%, or 99% identity thereto);~~₁

SEQ ID NOs: 7416 and 7418, respectively ~~(or a sequence having at least 85%, 90%, 95%, or 99% identity thereto);~~₁

SEQ ID NOs: 7417 and 7418, respectively ~~(or a sequence having at least 85%, 90%, 95%, or 99% identity thereto);~~₁

SEQ ID NOs: 7425 and 7418, respectively ~~(or a sequence having at least 85%, 90%, 95%, or 99% identity thereto);~~₁ or₁

SEQ ID NOs: 7428 and 7418, respectively ~~(or a sequence having at least 85%, 90%, 95%, or 99% identity thereto);~~₁ or₁

SEQ ID NOs: 7431 and 7418, respectively ~~(or a sequence having at least 85%, 90%, 95%, or 99% identity thereto);~~₁

9. The method of claim 8, wherein the VH and VL comprise amino acid sequences of:

SEQ ID NOs: 7420 and 7419, respectively;

SEQ ID NOs: 7423 and 7419, respectively;

SEQ ID NOs: 7411 and 7419, respectively;

SEQ ID NOs: 7412 and 7419, respectively;

SEQ ID NOs: 7413 and 7419, respectively;

SEQ ID NOs: 7414 and 7419, respectively;

SEQ ID NOs: 7415 and 7419, respectively;

SEQ ID NOs: 7416 and 7419, respectively;

SEQ ID NOs: 7417 and 7419, respectively;

SEQ ID NOs: 7425 and 7419, respectively;

SEQ ID NOs: 7428 and 7419, respectively;

SEQ ID NOs: 7431 and 7419, respectively;

SEQ ID NOs: 7420 and 7418, respectively;

SEQ ID NOs: 7423 and 7418, respectively;

[SEQ ID NOs: 7411 and 7418, respectively;](#)
[SEQ ID NOs: 7412 and 7418, respectively;](#)
[SEQ ID NOs: 7413 and 7418, respectively;](#)
[SEQ ID NOs: 7414 and 7418, respectively;](#)
[SEQ ID NOs: 7415 and 7418, respectively;](#)
[SEQ ID NOs: 7416 and 7418, respectively;](#)
[SEQ ID NOs: 7417 and 7418, respectively;](#)
[SEQ ID NOs: 7425 and 7418, respectively;](#)
[SEQ ID NOs: 7428 and 7418, respectively; or](#)
[SEQ ID NOs: 7431 and 7418, respectively.](#)

~~11,10.~~ [10.](#) The method of any one of claims ~~1-10,~~[1-9,](#) wherein the first antigen binding domain binds to ~~T-cell receptor beta chain constant domain 2 (TRBC2);~~[2](#), and wherein:

(i) the first antigen binding domain has a higher affinity for a T cell receptor comprising TRBC2 than for a T cell receptor not comprising TRBC2,~~optionally wherein the K_D for the binding between the first antigen binding domain and TRBC2 is no more than 40%, 30%, 20%, 10%, 1%, 0.1%, or 0.01% of the K_D for the binding between the first antigen binding domain and a T cell receptor not comprising TRBC2;~~

(ii) the first antigen binding domain has a higher affinity for a T cell receptor comprising TRBC2 than for a T cell receptor comprising TRBC1,~~optionally wherein the K_D for the binding between the first antigen binding domain and TRBC2 is no more than 40%, 30%, 20%, 10%, 1%, 0.1%, or 0.01% of the K_D for the binding between the first antigen binding domain and a T cell receptor comprising TRBC1; or,~~[or](#)

(iii) binding of the first antigen binding domain to TRBC2 on a lymphoma cell or lymphocyte, does not ~~appreciably~~[substantially](#) activate the lymphoma cell ~~or,~~[or](#) lymphocyte expression of a T cell activation marker, and/or expression of a cytokine.

~~12,11.~~ [11.](#) The method of any one of claims ~~1-11,~~[1-10,](#) wherein the first antigen binding domain binds to ~~T-cell receptor beta chain constant domain 2 (TRBC2);~~[2](#), and the polypeptide molecule binds to TRBC2 monovalently.

~~13,12.~~ [12.](#) The method of any one of claims ~~1-12,~~[1-11,](#) wherein the polypeptide molecule comprises a configuration ~~shown in any of FIGs. 30A-30D,~~[1-11,](#) wherein:

- (i) the polypeptide molecule comprises an anti-TRBC2 Fab and an anti-NKp30 scFv;
- (ii) the polypeptide molecule comprises an anti-TRBC2 Fab and an anti-NKp30 Fab;
- (iii) the polypeptide molecule comprises an anti-NKp30 Fab and an anti-TRBC2 scFv; or
- (iv) the polypeptide molecule comprises an anti-TRBC2 scFv and an anti-NKp30 scFv.

~~14.13.~~ The method of any one of claims ~~1-13, 1-12,~~ wherein the polypeptide molecule further comprises a dimerization module comprising one or more immunoglobulin chain constant regions comprising one or more of: a paired cavity-protuberance (“knob-in-a hole”), an electrostatic interaction, or a strand-exchange.

~~14.~~ The method of any one of claims ~~1-14, 1-13,~~ wherein the polypeptide molecule comprises:

~~15.~~ an anti-TRBC2 VH comprising an amino acid sequence ~~disclosed in any of Tables 21-25, or a sequence having at least 85%, 90%, 95%, or 99% % sequence identity thereto, and/or to SEQ ID NO: 7420,~~ an anti-NKp30 TRBC2 VL comprising an amino acid sequence ~~disclosed in any one of Tables 7, 8, 8A, 8B, 9, 10, 18, and 25, or a sequence having at least 85%, 90%, 95%, or 99% % sequence identity thereto.~~

~~16.~~ The method of any one of claims ~~1-15,~~ wherein the polypeptide molecule comprises:

~~(i) (i) to SEQ ID NO: 7419, an anti-TRBC2NKp30 VH of SEQ ID NO: 7420 (or a comprising an amino acid sequence having at least 85%, 90%, 95%, or 99% % sequence identity thereto), an anti-TRBC2 VL of SEQ ID NO: 7419 (or a sequence having at least 85%, 90%, 95%, or 99% identity thereto), an anti-NKp30-VH of to SEQ ID NO: 7302 (or a sequence having at least 85%, 90%, 95%, or 99% identity thereto), and, and an anti-NKp30 VL of comprising an amino acid sequence having at least 85% sequence identity to SEQ ID NO: 7309 (or a sequence having at least 85%, 90%, 95%, or 99% identity thereto);~~

~~(ii) or optionally,~~ an anti-TRBC2 VH comprising an amino acid sequence of SEQ ID NO: 7420 ~~(or a sequence having at least 85%, 90%, 95%, or 99% identity thereto),~~ an anti-TRBC2 VL comprising an amino acid sequence of SEQ ID NO: 7419 ~~(or a sequence having at least 85%, 90%, 95%, or 99% identity thereto),~~ and an anti-NKp30 scFv of SEQ ID NO: 7311 ~~(or a,~~ an anti-NKp30 VH comprising an amino acid sequence having at least 85%, 90%, 95%, or 99% identity thereto); or

~~(iii) SEQ ID NOs: 7438, 7439, and 7383 (or a sequence having at least 85%, 90%, 95%, or 99% identity thereto).~~

~~17.~~ The method of any one of claims ~~1-15,~~ wherein the polypeptide molecule comprises:

~~(i) an anti-TRBC2 VH of SEQ ID NO: 7423 (or a sequence having at least 85%, 90%, 95%, or 99% identity thereto), an anti-TRBC2 VL of SEQ ID NO: 7419 (or a sequence having at least 85%, 90%, 95%, or 99% identity thereto), an anti-NKp30-VH of SEQ ID NO: 7302 (or a sequence having at least 85%, 90%, 95%, or 99% identity thereto), and an anti-NKp30 VL comprising an amino acid sequence of SEQ ID NO: 7309 (or a sequence having at least 85%, 90%, 95%, or 99% identity thereto);~~

~~(ii) (ii)~~ an anti-TRBC2 VH comprising an amino acid sequence having at least 85% sequence identity to SEQ ID NO: 7420, an anti-TRBC2 VL comprising an amino acid sequence having at least 85%

sequence identity to SEQ ID NO: 7419, and an anti-NKp30 scFv comprising an amino acid sequence having at least 85% sequence identity to SEQ ID NO: 7311;

or optionally, an anti-TRBC2 VH comprising an amino acid sequence of SEQ ID NO: 7423
~~(or a sequence having at least 85%, 90%, 95%, or 99% identity thereto);~~7420, an anti-TRBC2
VL comprising an amino acid sequence of SEQ ID NO: 7419~~(or a sequence having at least~~
~~85%, 90%, 95%, or 99% identity thereto);~~, and an anti-NKp30 scFv comprising an amino
acid sequence of SEQ ID NO: 7311~~(or a sequence having at least 85%, 90%, 95%, or 99%~~
~~identity thereto); or;~~

(iii) an anti-TRBC2 VH having at least 85% sequence identity to SEQ ID NO: 7423, an anti-
TRBC2 VL having at least 85% sequence identity to SEQ ID NO: 7419, an anti-NKp30 VH
having at least 85% sequence identity to SEQ ID NO: 7302, and an anti-NKp30 VL having at least
85% sequence identity to SEQ ID NO: 7309;

or optionally, an anti-TRBC2 VH comprising an amino acid of SEQ ID NO: 7423, an anti-
TRBC2 VL comprising an amino acid of SEQ ID NO: 7419, an anti-NKp30 VH comprising
an amino acid of SEQ ID NO: 7302, and an anti-NKp30 VL comprising an amino acid of
SEQ ID NO: 7309;

(iv) an anti-TRBC2 VH having at least 85% sequence identity to SEQ ID NO: 7423, an anti-TRBC2
VL having at least 85% sequence identity to SEQ ID NO: 7419, and an anti-NKp30 scFv having at
least 85% sequence identity to SEQ ID NO: 7311;

or optionally, an anti-TRBC2 VH having at least 85% sequence identity to SEQ ID NO:
7423, an anti-TRBC2 VL having at least 85% sequence identity to SEQ ID NO: 7419, and an
anti-NKp30 scFv having at least 85% sequence identity to SEQ ID NO: 7311; or

(v) amino acid sequences that are at least 85% identical to SEQ ID NOs: 7440, 7439, and 7383~~(or a~~
~~sequence having at least 85%, 90%, 95%, or 99% identity thereto);~~

~~18. The method of any one of claims 1-3, wherein the first antigen binding domain binds to T cell receptor beta chain constant domain 1 (TRBC1), and wherein the first antigen binding domain comprises one or more CDRs, framework regions, variable regions, or antigen binding domains disclosed in any of Tables 3A-3B or 4, or a sequence having at least 85%, 90%, 95%, or 99% identity thereto.~~

~~19. The method of any one of claims 1-3, wherein the first antigen binding domain binds to T cell receptor beta chain constant domain 1 (TRBC1), and wherein the second antigen binding domain comprises one or more CDRs, framework regions, variable regions, or antigen binding domains disclosed in any one of Tables 8A-8B, 9, and 10, or a sequence having at least 85%, 90%, 95%, or 99% identity thereto.~~

~~20. The method of any one of claims 1-19, wherein the second antigen binding domain comprises one or more CDRs, framework regions, variable regions, or antigen binding domains disclosed in any one of Tables 7, 8, 8A, 8B, 9, 10, 18, and 25, or a sequence having at least 85%, 90%, 95%, or 99% identity thereto.~~

~~The method of any one of claims 1-20, or optionally, amino acid sequences comprising the sequences of SEQ ID NOs: 7440, 7439, and 7383; or~~

~~(vi) amino acid sequences having at least 85% sequence identity to: SEQ ID NOs: 7438, 7439, and 7383;~~

~~or optionally, amino acid sequences comprising the sequences of SEQ ID NOs: 7438, 7439, and 7383.~~

15. The method of any one of claims 1-14, wherein the second antigen binding domain comprises a VH comprising a heavy chain complementarity determining region 1 (VHCDR1), a VHCDR2, and a VHCDR3; and a VL comprising a light chain complementarity determining region 1 (VLCDR1), a VLCDR2, and a VLCDR3,

~~21.~~ wherein the VHCDR1, VHCDR2, and VHCDR3 of the second antigen binding domain comprise the amino acid sequences of:

SEQ ID NOs: 7313, 6001, and 7315, respectively;

SEQ ID NOs: 7313, 6001, and 6002, respectively;

SEQ ID NOs: 7313, 6008, and 6009, respectively;

SEQ ID NOs: 7313, 7385, and 7315, respectively;

SEQ ID NOs: 7313, 7318, and 6009, respectively;

SEQ ID NOs: ~~C019~~, ~~C021~~375, 377, and ~~C023~~379, respectively;

SEQ ID NOs: ~~C033~~, ~~C035~~389, 391, and ~~C037~~393, respectively;

SEQ ID NOs: ~~C047~~, ~~C049~~403, 405, and ~~C051~~407, respectively;

SEQ ID NOs: ~~C061~~, ~~C063~~417, 419, and ~~C065~~421, respectively;

SEQ ID NOs: ~~C075~~, ~~C077~~431, 433, and ~~C079~~435, respectively;

SEQ ID NOs: ~~C089~~, ~~C091~~445, 447, and ~~C093~~449, respectively;

SEQ ID NOs: ~~C103~~, ~~C105~~459, 461, and ~~C107~~463, respectively; or

SEQ ID NOs: ~~C116~~, ~~C118~~472, 474, and ~~C120~~476, respectively; ~~and/or~~

~~22. The method of claim 21,~~ wherein the VLCDR1, VLCDR2, and VLCDR3 of the second antigen binding domain comprise the amino acid sequences of:

SEQ ID NOs: 7326, 7327, and 7329, respectively;

SEQ ID NOs: 6063, 6064, and 7293, respectively;

SEQ ID NOs: 6070, 6071, and 6072, respectively;
 SEQ ID NOs: 6070, 6064, and 7321, respectively;
 SEQ ID NOs: ~~C026, C028~~382, 384, and ~~C030~~386, respectively;
 SEQ ID NOs: ~~C040, C042~~396, 398, and ~~C044~~400, respectively;
 SEQ ID NOs: ~~C054, C056~~410, 412, and ~~C058~~414, respectively;
 SEQ ID NOs: ~~C068, C070~~424, 426, and ~~C072~~428, respectively;
 SEQ ID NOs: ~~C082, C084~~438, 440, and ~~C086~~442, respectively;
 SEQ ID NOs: ~~C096, C098~~452, 454, and ~~C100~~456, respectively;
 SEQ ID NOs: ~~C110, C112~~466, 468, and ~~C113~~469, respectively; or
 SEQ ID NOs: ~~C123, C125~~479, 481, and ~~C127~~483, respectively.

~~23, 16.~~ The method of claim ~~21 or 22,~~15, wherein the VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, and VLCDR3 of the second antigen binding domain comprise the amino acid sequences of:

SEQ ID NOs: 7313, 6001, 7315, 7326, 7327, and 7329, respectively;
 SEQ ID NOs: 7313, 6001, 6002, 6063, 6064, and 7293, respectively;
 SEQ ID NOs: 7313, 6008, 6009, 6070, 6071, and 6072, respectively;
 SEQ ID NOs: 7313, 7385, 7315, 6070, 6064, and 7321, respectively;
 SEQ ID NOs: 7313, 7318, 6009, 6070, 6064, and 7321, respectively;
 SEQ ID NOs: ~~C019, C021, C023, C026, C028~~375, 377, 379, 382, 384, and ~~C030~~386, respectively;
 SEQ ID NOs: ~~C033, C035, C037, C040, C042~~389, 391, 393, 396, 398, and ~~C044~~400, respectively;
 SEQ ID NOs: ~~C047, C049, C051, C054, C056~~403, 405, 407, 410, 412, and ~~C058~~414, respectively;
 SEQ ID NOs: ~~C061, C063, C065, C068, C070~~417, 419, 421, 424, 426, and ~~C072~~428, respectively;
 SEQ ID NOs: ~~C075, C077, C079, C082, C084~~431, 433, 435, 438, 440, and ~~C086~~442, respectively;
 SEQ ID NOs: ~~C089, C091, C093, C096, C098~~445, 447, 449, 452, 454, and ~~C100~~456, respectively;
 SEQ ID NOs: ~~C103, C105, C107, C110, C112~~459, 461, 463, 466, 468, and ~~C113~~469, respectively; or
 SEQ ID NOs: ~~C116, C118, C120, C123, C125~~472, 474, 476, 479, 481, and ~~C127~~483, respectively.

~~24, 17.~~ The method of ~~any one of claims 21-23,~~claim 15 or 16, wherein:

- (i) ~~(i)~~ the VH of the second antigen binding domain comprises an amino acid sequence having at least 85% identity to any one sequence selected from the group consisting of SEQ ID NOs: 7302, 7298, 7300, 7301, 7303, and 7304 ~~(or a sequence having at least 85%, 90%, 95%, or 99% identity thereto)~~ and/or the VL of the second antigen binding domain comprises an amino acid sequence having at least 85% identity to any one sequence selected from the group consisting of SEQ ID NOs: 7309, 7305, 7299, and 7306-7308 ~~(or a sequence having at least 85%, 90%, 95%, or 99% identity thereto);~~

~~(ii) or optionally,~~ the VH of the second antigen binding domain comprises ~~an~~any one amino acid sequence selected from the group consisting of SEQ ID NOs: ~~6121~~7302, 7298, 7300, 7301, 7303, and ~~6123-6128 (or a sequence having at least 85%, 90%, 95%, or 99% identity thereto)~~7304, and/or the VL of the second antigen binding domain comprises ~~an~~any one amino acid sequence selected from the group consisting of SEQ ID NOs: ~~7294 or 6137-6141 (or a sequence~~7309, 7305, 7299, and 7306-7308;

(ii) the VH of the second antigen binding domain comprises an amino acid sequence having at least 85% identity to any one sequence selected from the group consisting of SEQ ID NOs: 6121 and 6123-6128 and/or the VL of the second antigen binding domain comprises an amino acid sequence having at least 85%, 90%, 95%, or 99% identity thereto); or to any one sequence selected from the group consisting of SEQ ID NOs: 7294 and 6137-6141;

~~(iii) the VH of the second antigen binding domain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 6122 and 6129-6134 (or a sequence having at least 85%, 90%, 95%, or 99% identity thereto) and/or the VL of the second antigen binding domain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 6136 or 6142-6147 (or a sequence having at least 85%, 90%, 95%, or 99% identity thereto); or~~

~~(iv) or optionally,~~ the VH of the second antigen binding domain comprises ~~an~~any one amino acid sequence selected from the group consisting of SEQ ID NOs: ~~C001-C008 (or a sequence having at least 85%, 90%, 95%, or 99% identity thereto)~~6121 and 6123-6128 and/or the VL of the second antigen binding domain comprises ~~an~~any one amino acid sequence selected from the group consisting of SEQ ID NOs: ~~C009-C016 (or a sequence having at least 85%, 90%, 95%, or 99% identity thereto)~~7294 and 6137-6141;

~~24. The method of any one of claims 21-24, wherein the VH and VL of the second antigen binding domain comprise the amino acid sequences of:~~

(iii) SEQ ID NOs: 7302 and 7309, respectively (or a the VH of the second antigen binding domain comprises an amino acid sequence having at least 85% identity to any one sequence selected from the group consisting of SEQ ID NOs: 6122 and 6129-6134 and/or the VL of the second antigen binding domain comprises an amino acid sequence having at least 85% identity to any one sequence selected from the group consisting of SEQ ID NOs: 6136 and 6142-6147;

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

(iv) the VH of the second antigen binding domain comprises an amino acid sequence having at least 85% identity to any one sequence selected from the group consisting of SEQ ID NOs: 357-364 (and/or the VL of the second antigen binding domain comprises an amino acid sequence having at least 85% identity to any one sequence selected from the group consisting of SEQ ID NOs: 365-372; or optionally, the VH of the second antigen binding domain comprises an amino acid sequence having at least 85%, 90%, 95%, or 99% identity thereto); or

SEQ ID NOs: 7302 and 7305, respectively (or to any one sequence selected from the group consisting of SEQ ID NOs: 357-364 and/or the VL of the second antigen binding domain comprises an amino acid sequence having at least 85%, 90%, 95%, or 99% identity thereto); to any one sequence selected from the group consisting of SEQ ID NOs: 365-372.

18. The method of any one of claims ~~21-25~~, 15-17, wherein the VH and VL of the second antigen binding domain comprise amino acid sequences having at least 85% sequence identity to:

SEQ ID NOs: 7302 and 7309, respectively ;

SEQ ID NOs: 7302 and 7305, respectively;

or

~~25.~~ wherein the second antigen binding domain ~~comprise the~~ comprises an amino acid sequences of:

SEQ ID NO: 7311 or 7310 (or a sequence having at least 85%, 90%, 95%, or 99% identity thereto);

SEQ ID NO: 6187 or 6188 (or a sequence having at least 85%, 90%, 95%, or 99% identity thereto);

SEQ ID NO: 6189 or % sequence identical to any one sequence selected from the group consisting of SEQ ID NOs: 7311, 7310, 6187-6190 (or a sequence having at least 85%, 90%, 95%, or 99% identity thereto); or, 373, and 485-491.

19. ~~any of~~ The method of claim 18, wherein the VH and VL of the second antigen binding domain comprise amino acid sequences of:

SEQ ID NOs: ~~C017-C024~~, 7302 and 7309, respectively;

SEQ ID NOs: 7302 and 7305, respectively;

or

wherein the second antigen binding domain comprises any one amino acid sequence selected from the group consisting of SEQ ID NOs: 7311, 7310, 6187-6190, 373, and 485-491.

~~26.~~ The method of any one of claims ~~1-26~~, further comprising:

~~responsive to identifying the subject as a candidate for treatment using a multifunctional molecule comprising an antigen binding domain that binds to TRBC2, treating the subject with a multifunctional molecule as described herein.~~

~~28,20. The method of any one of claims 1-27, 1-19,~~ wherein the cancer is leukemia or lymphoma.

~~29,21.~~ The method of any one of claims ~~1-28,1-19,~~ wherein the cancer is selected from 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 Sézary syndrome), Follicular lymphoma, Lymphoplasmacytic lymphoma/Waldenström 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.

~~30. The method of any one of claims 1-29, wherein the cancer is Peripheral T-cell lymphoma (PTCL).~~

~~31. A method of detecting TRBC1 or TRBC2 in a sample or subject, comprising:~~

~~contacting the sample or subject with an anti-TRBC1 antibody molecule described herein or an anti-TRBC2 antibody molecule described herein; and~~

~~detecting formation of a complex between the antibody molecule and the sample or subject, thereby detecting TRBC1 or TRBC2.~~

~~35. The method of claim 31, wherein TRBC1 or TRBC2 is detected *in vitro* or *in vivo*.~~

~~36. The method of claim 31 or 32, further comprising contacting a reference sample or subject with the antibody molecule; and detecting formation of a complex between the antibody molecule and the reference sample or subject, wherein a change in the formation of the complex in the sample or subject, relative to the reference sample or subject is indicative of the presence of TRBC1 or TRBC2 in the sample or subject.~~

~~37. The method of any one of claims 31-33, further comprising obtaining a sample from a subject.~~

~~38. The method of any one of claims 31-34, 1, wherein the sample comprises one or more of plasma, tissue, biopsy, blood, PBMCs, bone marrow, and/or lymphatic tissue.~~

~~39. The method of any one of claims 31-35, wherein the sample has not been frozen and/or fixed.~~

~~40. The method of any one of claims 31-35, wherein the sample has been frozen and/or fixed.~~

~~41. The method of any one of claims 31-37, wherein the subject has, or is at risk of having, a disease or disorder described herein.~~

~~42. The method of any one of claims 31-38, further comprising performing a flow analysis.~~

- ~~43. The method of any one of claims 31-39, further comprising assessing T cell clonality.~~
- ~~44. The method of any one of claims 31-40, further comprising measuring the level of TRBC1+ or TRBC2+ cells from the biological sample.~~
- ~~45. The method of any one of claims 31-41, further comprising measuring the intracellular level of TRBC1 or TRBC2.~~
- ~~46. The method of any one of claims 31-42, further comprising measuring the membrane level of TRBC1 or TRBC2.~~
- ~~47. The method of any one of claims 31-43, further comprising evaluating the subject for a change in prognosis, severity, or presence or absence of a disease or disorder.~~
- ~~48. The method of any one of claims 31-44, wherein the antibody molecule is detectably labeled.~~
- ~~49. A method of evaluating a subject, comprising:~~
~~contacting a sample from the subject with an anti-TRBC1 antibody molecule described herein or an anti-TRBC2 antibody molecule described herein; and~~
~~detecting formation of a complex between the antibody molecule and the sample,~~
~~thereby evaluating the subject.~~
- ~~53. The method of claim 46, wherein the subject has, or is at risk of having, a disease or disorder described herein.~~
- ~~54. The method of claim 46 or 47, wherein the subject has not been treated with an antibody molecule described herein.~~
- ~~55. The method of claim 46 or 47, wherein the subject has been treated with an antibody molecule described herein.~~
- ~~56. A kit comprising an anti-TRBC1 antibody molecule described herein or an anti-TRBC2 antibody molecule described herein and instructions for use in a method of detecting TRBC1 or TRBC2 in a sample or subject.~~
22. A method of identifying a subject in need of treatment for cancer comprising determining that a peripheral blood mononuclear cell (PBMC)-derived T cell population~~obtained from the subject,~~
- 57.23. The method of claim 22, the method further comprises determining whether the PBMC-derived T cell population has a monotypia and specificity for TRBC1 or TRBC2,

wherein the monotypia and specificity for TRBC1 or TRBC2 in the PBMC-derived T cell population indicates that the subject has a T cell malignancy, thereby identifying the subject as a candidate for treatment for the cancer.

24. The method of any one of claims 1-23, wherein a determination that the subject has cancer cells that express a T cell receptor comprising TRBC2 identifies the subject as not being as a candidate for treatment using a multifunctional molecule comprising an antigen binding domain that binds to TRBC1.

25. The method of any one of claims 1-23, wherein a determination that the subject has cancer cells that express a T cell receptor comprising TRBC1 identifies the subject as not being as a candidate for treatment using a multifunctional molecule comprising an antigen binding domain that binds to TRBC2.

26. Use of a pharmaceutical composition comprising a polypeptide molecule in the manufacture of a medicament for treating cancer in a subject in need thereof, wherein the polypeptide molecule comprises:

(i) a first antigen binding domain that binds to T cell receptor beta chain constant domain 1 (TRBC1) or T cell receptor beta chain constant domain 2 (TRBC2), and

(ii) a second antigen binding domain that binds to NKp30;

wherein:

the subject has been identified as a candidate for treatment using the polypeptide molecule, based at least in part on determination that the subject has cancer cells that express a T cell receptor comprising TRBC1 or TRBC2.