

ANTI-TCR ANTIBODY MOLECULES AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application 62/957,024 filed on
5 January 3, 2020, and U.S. Provisional Application 63/070,596 filed on August 26, 2020, the
entire contents of each of which are hereby incorporated by reference.

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted
10 electronically in ASCII format and is hereby incorporated by reference in its entirety. Said
ASCII copy, created on January 29, 2021, is named 53676-736_601_SL.txt and is 1,197,327
bytes in size.

BACKGROUND

Current molecules designed to redirect T cells to promote tumor cell lysis for cancer
15 immunotherapy typically target the CD3 epsilon (CD3e) subunit of the T cell receptor (TCR).
However, there are limitations to this approach. Previous studies have shown that, *e.g.*, low
doses of anti-CD3e monoclonal antibody (mAb) can cause T cell dysfunction and exert
immunosuppressive effects. In addition, anti-CD3e mAbs bind to all T cells and thus activate a
large number of T cells. Such non-physiological massive activation of T cells by these anti-
20 CD3e mAbs can result in the production of proinflammatory cytokines such as IFN-gamma, IL-
1-beta, IL-6, IL-10 and TNF-alpha, causing a “cytokine storm” known as the cytokine release
syndrome (CRS), which is also associated with neurotoxicity (NT). Thus, it might be
advantageous to develop antibodies that avoid or reduce CRS and/or NT.

25 SUMMARY OF THE INVENTION

Disclosed herein are, *inter alia*, antibody molecules directed to the variable chain of the
beta subunit of TCR (TCR β V) which bind and, *e.g.*, activate or expand, T cells, *e.g.*, a subset of
T cells (“anti-TCR β V antibody molecules”). In some embodiments, the anti-TCR β V antibody
molecules disclosed herein result in a cytokine profile, *e.g.*, a cytokine secretion profile, that
30 differs from that of a T cell engager that binds to a receptor or molecule other than a TCR β V
region (“a non-TCR β V-binding T cell engager”). In some embodiments, the anti-TCR β V
antibody molecules disclosed herein result in lesser, minimal, or no production of cytokines
associated with cytokine release syndrome (CRS), *e.g.*, IL-6, IL-1beta, IL-10 and TNF alpha;
and enhanced and/or delayed production of IL-2 and IFN-gamma. In some embodiments, the

anti-TCR β V antibodies disclosed herein result in expansion of an immune cell, *e.g.*, a T cell, a tumor infiltrating lymphocyte (TIL), an NK cell, or other immune cells (*e.g.*, as described herein). Also provided herein are methods of making said anti-TCR β V antibody molecules, and methods of using said anti-TCR β V antibody molecules including, methods of using an anti-TCR β V antibody molecule for expanding an immune cell or an immune cell population, and
5 method of using an anti-TCR β V antibody molecule for treating cancer, including the use as

combination therapy with TIL and immune checkpoint therapeutics. This disclosure further provides multispecific molecules, *e.g.*, bispecific molecules, comprising said anti-TCR β V antibody molecules. In some embodiments, compositions comprising anti-TCR β V antibody molecules of the present disclosure, can be used, *e.g.*, to activate and/or redirect T cells to promote tumor cell lysis for cancer immunotherapy. In some embodiments, compositions comprising anti-TCR β V antibody molecules as disclosed herein limit the unwanted side-effects of CRS and/or NT, *e.g.*, CRS and/or NT associated with anti-CD3e targeting.

In some embodiments, the anti-TCR β V antibody molecules disclosed herein result in lesser, minimal, or no production of cytokines associated with cytokine release syndrome (CRS), *e.g.*, IL-6, IL-1 β , IL-10 and TNF α ; and enhanced and/or delayed production of IL-2 and IFN- γ , compared with an anti-CD3 antibody molecule (*e.g.*, a low affinity anti-CD3 antibody molecule). In some embodiments, administration of the anti-TCR β V antibody molecules disclosed herein in a subject results in reduced cytokine release syndrome (CRS) (*e.g.*, lesser duration of CRS or no CRS), a reduced severity of CRS (*e.g.*, absence of severe CRS, *e.g.*, CRS grade 4 or 5), reduced neurotoxicity (NT), or a reduced severity of NT, compared with similar administration of an anti-CD3 antibody molecule (*e.g.*, a low affinity anti-CD3 antibody molecule).

Accordingly, provided herein are, anti-TCR β V antibody molecules, multispecific or multifunctional molecules (*e.g.*, multispecific or multifunctional antibody molecules) (also referred to herein as a “composition”) that comprise anti-TCR β V antibody molecules, nucleic acids encoding the same, methods of producing the aforesaid molecules, pharmaceutical compositions comprising aforesaid molecules, and methods of treating a disease or disorder, *e.g.*, cancer, using the aforesaid molecules. The antibody molecules and pharmaceutical compositions disclosed herein can be used (alone or in combination with other agents or therapeutic modalities) to treat, prevent and/or diagnose disorders and conditions, *e.g.*, cancer, *e.g.*, as described herein.

In one aspect, provided herein is a molecule comprising an antigen binding domain that binds to T cell receptor beta variable region (TCR β V), wherein the antigen binding domain comprises:

- (i) a heavy chain variable region (VH) comprising a heavy chain complementarity determining region 1 (HC CDR1), a heavy chain complementarity determining region 2 (HC CDR2), and a heavy chain complementarity determining region 3 (HC CDR3) of SEQ ID NO: 1100, and a light chain variable region (VL) comprising a light chain complementarity determining region 1 (LC CDR1), a light chain complementarity

- determining region 2 (LC CDR2), and a light chain complementarity determining region 3 (LC CDR3) of SEQ ID NO: 1101;
- (ii) a VH comprising a HC CDR1, a HC CDR2, and a HC CDR3 of SEQ ID NO: 1346, and a VL comprising a LC CDR1, a LC CDR2, and a LC CDR3 of SEQ ID NO: 1347 or
5 SEQ ID NO: 1349;
- (iii) a VH comprising a HC CDR1, a HC CDR2, and a HC CDR3 of SEQ ID NO: 1348, and a VL comprising a LC CDR1, a LC CDR2, and a LC CDR3 of SEQ ID NO: 1349;
- (iv) a VH comprising a HC CDR1, a HC CDR2, and a HC CDR3 of SEQ ID NO: 1350, and a VL comprising a LC CDR1, a LC CDR2, and a LC CDR3 of SEQ ID NO: 1349,
10 SEQ ID NO: 1351, SEQ ID NO: 1353, SEQ ID NO: 1365, SEQ ID NO: 1367, or SEQ ID NO: 1369;
- (v) a VH comprising a HC CDR1, a HC CDR2, and a HC CDR3 of SEQ ID NO: 1356, and a VL comprising a LC CDR1, a LC CDR2, and a LC CDR3 of SEQ ID NO: 1357;
- (vi) a VH comprising a HC CDR1, a HC CDR2, and a HC CDR3 of SEQ ID NO: 1360
15 or SEQ ID NO: 1362, and a VL comprising a LC CDR1, a LC CDR2, and a LC CDR3 of SEQ ID NO: 1361;
- (vii) a VH comprising a HC CDR1, a HC CDR2, and a HC CDR3 of SEQ ID NO: 1370, and a VL comprising a LC CDR1, a LC CDR2, and a LC CDR3 of SEQ ID NO: 1365, SEQ ID NO: 1367, or SEQ ID NO: 1369;
- (viii) a VH comprising a HC CDR1, a HC CDR2, and a HC CDR3 of SEQ ID NO: 1112,
20 SEQ ID NO: 1113, SEQ ID NO: 1114, SEQ ID NO: 1115, or SEQ ID NO: 1116, and a VL comprising a LC CDR1, a LC CDR2, and a LC CDR3 of SEQ ID NO: 1111;
- (ix) a VH comprising a HC CDR1, a HC CDR2, and a HC CDR3 of SEQ ID NO: 1310 or SEQ ID NO: 1311, and a VL comprising a LC CDR1, a LC CDR2, and a LC CDR3
25 of SEQ ID NO: 1313;
- (x) a VH comprising a HC CDR1, a HC CDR2, and a HC CDR3 of SEQ ID NO: 1312, and a VL comprising a LC CDR1, a LC CDR2, and a LC CDR3 of SEQ ID NO: 1314;
or
- (xi) a single chain variable fragment (scfv) comprising a HC CDR1, a HC CDR2, a HC
30 CDR3, a LC CDR1, a LC CDR2, and a LC CDR3 of any one sequence selected from the group consisting of SEQ ID NOs: 1309, 1326-1337, and 110.

In one aspect, provided herein is a recombinant polynucleotide comprising a sequence encoding the molecule as described herein.

In one aspect, provided herein is a pharmaceutical composition comprising the molecule as described herein, and a pharmaceutically acceptable carrier, excipient, or stabilizer for use in therapy.

5 In one aspect, provided herein is a use of a pharmaceutical composition comprising the molecule as described herein in the manufacture of a medicament for treating cancer in a subject in need thereof, wherein an effective amount of the molecule is to be administered to the subject.

In one aspect, provided herein is a of a composition comprising the molecule as described herein in the manufacture of a medicament for modulating an immune response in a subject in need thereof, optionally, wherein an effective amount of the molecule expands an immune
10 cell population, optionally, wherein the expansion occurs *in vivo* or *ex vivo*.

In one aspect, the disclosure provides an antibody molecule, e.g., a non-murine, e.g., a human-like (e.g., a human, or humanized antibody molecule), which binds, e.g., specifically binds, to a T cell receptor beta variable (TCR β V) region.

In some embodiments, the anti-TCRBV antibody molecule comprises an antigen binding
15 domain of an antibody disclosed in any of Tables 1-2, or 10-13, or a sequence with at least 85%, 90%, 95%, 96%, 97%, 98%, or 99% identity thereto. In some embodiments, the anti-TCRBV antibody molecule comprises a leader sequence comprising the amino acid sequence of SEQ ID

Table 9: Alignment of TCRBV amino acid sequences (SEQ ID NOS 3457-3516, respectively, in order of appearance)

	FR1-IMGT				CDR1-IMGT				FR2-IMGT				CDR2-IMGT				FR3-IMGT				CDR3-IMGT																							
	(1-26)				(27-38)				(39-55)				(56-65)				(66-104)				(105-117)																							
Gene	A				B				BC				C				C'				C'C"				C"				D				E				F				FG			
	(1-15)				(16-26)				(27-38)				(39-46)				(47-55)				(56-65)				(66-74)				(75-84)				(85-96)				(97-104)							
	—————>				—————>				—————>				—————>				—————>				—————>				—————>				—————>				—————>				—————>							
	1	10	15	16	23	26	27	38	3941	46	47	55	56	65	66	74	75	84	85	89	96	97	104	105																				
						..																																						
TRBV1	DTGITQTPKYLVTAM	GSKRTMKREHL	GH	DS	MYWYRQKA	KKSLEFMFY	YNC	KEF	IENKTVP.N	HFTPECF.DS	SRLYLHVVALQQ	EDSAAYLC	TSSQ																															
TRBV2	EPEVTQTPSHQVTQM	GQEVILRCVPI	SNH	LY	FYWYRQIL	GQKVEFLVS	FYN	NEI	SEKSEIFDD	QFSVERP.DG	SNFTLKIRSTKL	EDSAMYFC	ASSE																															
TRBV3-1	DTAVSQTPKYLVTQM	GNDKSIKCEQN	LGH	DT	MYWYKQDS	KKFLKIMFS	YNN	KEL	IINETVP.N	RFSPKSP.DK	AHLNLHINSLEL	GDSAVYFC	ASSQ																															
TRBV3-2	DTAVSQTPKYLVTQM	GKKESLK*EQN	LGH	NA	MYWYKQDS	KKFLKTMFI	YSN	KEP	ILNETVP.N	RFSPPDSP.DK	AHLNLHINSLEL	GDSAVYFC	ASSQ																															
TRBV4-1	DTEVTQTPKHLVMGM	TNKSCLKCEQH	MGH	RA	MYWYKQKA	KKPPELMFV	YSY	EKL	SINESVP.S	RFSPECF.NS	SLNLHLHALQP	EDSALYLC	ASSQ																															
TRBV4-2	ETGVTQTPRHLVMGM	TNKSCLKCEQH	LGH	NA	MYWYKQSA	KKPLELMFV	YNF	KEQ	TENNSVP.S	RFSPECF.NS	SHLFLHLHTLQP	EDSALYLC	ASSQ																															
TRBV4-3	ETGVTQTPRHLVMGM	TNKSCLKCEQH	LGH	NA	MYWYKQSA	KKPLELMFV	YSL	EER	VENNSVP.S	RFSPECF.NS	SHLFLHLHTLQP	EDSALYLC	ASSQ																															
TRBV5-1	KAGVTQTPRYLIKTR	GQQVTLRCSPI	SGH	RS	VSWYQQTP	GQGLQFLFE	YFS	ETQ	RNKGNFP.G	RFSGRQF.SN	SRSEMNVSTLEL	GDSALYLC	ASSL																															
TRBV5-3	EAGVTQSPTHLIKTR	GQQVTLRCSPI	SGH	SS	VSWYQQAP	GQGPQFIFE	YAN	ELR	RSEGNFP.N	RFSGRQF.HD	CCSEMNVSALEL	GDSALYLC	ARSL																															
TRBV5-4	ETGVTQSPTHLIKTR	GQQVTLRCSQ	SGH	NT	VSWYQQAL	GQGPQFIFQ	YYR	EEE	NGRGNFP.P	RFSGLQF.PN	YSSELNVNALEL	DDSALYLC	ASSL																															
TRBV5-5	DAGVTQSPTHLIKTR	GQQVTLRCSPI	SGH	KS	VSWYQQVL	GQGPQFIFQ	YYE	KEE	RGRGNFP.D	RFSARQF.PN	YSSELNVNALLL	GDSALYLC	ASSL																															
TRBV5-6	DAGVTQSPTHLIKTR	GQQVTLRCSPK	SGH	DT	VSWYQQAL	GQGPQFIFQ	YYE	EEE	RQGRNFP.D	RFSGHQF.PN	YSSELNVNALLL	GDSALYLC	ASSL																															
TRBV5-7	DAGVTQSPTHLIKTR	GQHVTLRCSPI	SGH	TS	VSSYQQAL	GQGPQFIFQ	YYE	KEE	RGRGNFP.D	QFSGHQF.PN	YSSELNVNALLL	GDSALYLC	ASSL																															
TRBV5-8	EAGVTQSPTHLIKTR	GQQATLRCSPI	SGH	TS	VYWYQQAL	GLGLQFLLW	YDE	GEE	RNRGNFP.P	RFSGRQF.PN	YSSELNVNALEL	EDSALYLC	ASSL																															
TRBV6-1	NAGVTQTPKFQVLKT	GQSMTLQCAQD	MNH	NS	MYWYRQDP	GMGLRLIYY	SAS	EGT	TDKGEVP.N	GYNVSRL.NK	REFSLRLESAAAP	SQTSVYFC	ASSE																															
TRBV6-2	NAGVTQTPKFRVLKT	GQSMTLLCAQD	MNH	EY	MYWYRQDP	GMGLRLIHY	SVG	EGT	TAKGEVP.D	GYNVSRL.KK	QNFLGLLESAAAP	SQTSVYFC	ASSY																															
TRBV6-3	NAGVTQTPKFRVLKT	GQSMTLLCAQD	MNH	EY	MYWYRQDP	GMGLRLIHY	SVG	EGT	TAKGEVP.D	GYNVSRL.KK	QNFLGLLESAAAP	SQTSVYFC	ASSY																															
TRBV6-4	IAGITQAPTSQILAA	GRMTLRCQD	MRH	NA	MYWYRQDL	GLGLRLIHY	SNT	AGT	TDKGEVP.D	GYSVSRA.NT	DDFPLTLASAVP	SQTSVYFC	ASSD																															
TRBV6-5	NAGVTQTPKFQVLKT	GQSMTLQCAQD	MNH	EY	MSWYRQDP	GMGLRLIHY	SVG	AGI	TDQGEVP.N	GYNVSRS.TT	EDFPLRLLSAAAP	SQTSVYFC	ASSY																															
TRBV6-6	NAGVTQTPKFRILKI	GQSMTLQCTQD	MNH	NY	MYWYRQDP	GMGLKLIYY	SVG	AGI	TDKGEVP.N	GYNVSRS.TT	EDFPLRLELAAP	SQTSVYFC	ASSY																															
TRBV6-7	NAGVTQTPKFHVLT	GQSMTLLCAQD	MNH	EY	MYRYRQDP	GKGLRLIYY	SVA	AAL	TDKGEVP.N	GYNVSRS.NT	EDFPLKLESAAAP	SQTSVYFC	ASSY																															
TRBV6-8	NAGVTQTPKFHILKT	GQSMTLQCAQD	MNH	GY	MSWYRQDP	GMGLRLIYY	SAA	AGT	TDK.EVP.N	GYNVSRL.NT	EDFPLRLVSAAP	SQTSVYLC	ASSY																															
TRBV6-9	NAGVTQTPKFHILKT	GQSMTLQCAQD	MNH	GY	LSWYRQDP	GMGLRRIHY	SVA	AGI	TDKGEVP.D	GYNVSRS.NT	EDFPLRLESAAAP	SQTSVYFC	ASSY																															
TRBV7-1	GAGVSQSLRHKVAKK	GKDVALRYDPI	SGH	NA	LYWYRQSL	GQGLEFPYI	FQG	KDA	ADKSGLPRD	RFSAQRS.EG	SISTLKFORQQ	GDLAVYLC	ASSS																															
TRBV7-2	GAGVSQSPSNKVTEK	GKDVELRCDPI	SGH	TA	LYWYRQSL	GQGLEFLIY	FQG	NSA	PKSGLPSD	RFSAERT.GG	SVSTLTIQRTQQ	EDSAVYLC	ASSL																															
TRBV7-3	GAGVSQTPSNKVTEK	GKYVELRCDPI	SGH	TA	LYWYRQSL	GQGPFLIYI	FQG	TGA	ADDSGLPND	RFFAVRP.EG	SVSTLKIQRTER	GDSAVYLC	ASSL																															
TRBV7-4	GAGVSQSPRYKVAKR	GRDVALRCDSI	SGH	VT	LYWYRQTL	GQGSEVLTY	SQS	DAQ	RDKSGRPSG	RFSAERP.ER	SVSTLKIQRTEQ	GDSAVYLC	ASSL																															
TRBV7-6	GAGVSQSPRYKVTKR	GQDVALRCDPI	SGH	VS	LYWYRQAL	GQGPFLTYI	FNY	EAQ	QDKSGLPND	RFSAERP.EG	SISTLTIQRTAQ	RDSAMYRC	ASSL																															
TRBV7-7	GAGVSQSPRYKVTKR	GQDVTLRCDPI	SSH	AT	LYWYQQAL	GQGPFLTYI	FNY	EAQ	PKSGLPSD	RFSAERP.EG	SISTLTIQRTAQ	RDSAMYRC	ASSL																															
TRBV7-8	GAGVSQSPRYKVAKR	GQDVALRCDPI	SGH	VS	LFWYQQAL	GQGPFLTYI	FQN	EAQ	LDKSGLPSD	RFFAERP.EG	SVSTLKIQRTEQ	EDSAVYLC	ASSL																															
TRBV7-9	DTGVSQNPRLHKITKR	GQNVTRCDPI	SEH	NR	LYWYRQTL	GQGPFLTYI	FQN	EAQ	LEKSRLLED	RFSAERP.KG	SFSTLEIQRTEQ	GDSAMYLC	ASSL																															
TRBV9	DSGVTQTPKHLITAT	GQRVTLRCSPR	SGD	LS	VYWYQQSL	DQGLQFLIQ	YYN	GEE	RAKNIL.E	RFSAQQF.PD	LHSELNLSLEL	GDSALYFC	ASSV																															
TRBV10-1	DAEITQSPRHKITET	GRQVTLACHQT	WNH	NN	MFWYRQDL	GHGLRLIHY	SYG	VQD	TNKGEVS.D	GYSVRS.NT	EDLPLTLESAAAS	SQTSVYFC	ASSE																															
TRBV10-2	DAGITQSPRYKITET	GRQVTLCHQQT	WSH	SY	MFWYRQDL	GHGLRLIYY	SAA	ADI	TDKGEVP.D	GYSVRS.KT	ENFPLTLESATR	SQTSVYFC	ASSE																															
TRBV10-3	DAGITQSPRHKVTE	GTPVTLRCHQT	ENH	RY	MYWYRQDP	GHGLRLIHY	SYG	VKD	TDKGEVS.D	GYSVRS.KT	EDFLLTLESATS	SQTSVYFC	AISE																															
TRBV11-1	EAEVAQSPRYKITEK	SQAVAFWCNPI	SGH	AT	LYWYRQIL	GQGPPELLVQ	FQD	ESV	VDSQLPKD	RFSAERL.KG	VDSTLKIQAEL	GDSAMYLC	ASSL																															
TRBV11-2	EAGVAQSPRYKIIKE	RQSVAFWCNPI	SGH	AT	LYWYQQIL	GQGPKLLIQ	FQN	NGV	VDSQLPKD	RFSAERL.KG	VDSTLKIQPAKL	EDSAVYLC	ASSL																															

a VL domain comprising the amino acid sequence of SEQ ID NO: 29, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ ID NO: 29, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 29.

5 In some embodiments, the anti-TCR β V antibody molecule, *e.g.*, anti-TCR β V12 antibody molecule comprises:

a VH domain comprising the amino acid sequence of SEQ ID NO: 23, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ ID NO: 23, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 23; and

10 a VL domain comprising the amino acid sequence of SEQ ID NO: 30, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ ID NO: 30, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 30.

15 In some embodiments, the anti-TCR β V antibody molecule, *e.g.*, anti-TCR β V12 antibody molecule comprises:

a VH domain comprising the amino acid sequence of SEQ ID NO: 24 or 25, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ ID NO: 24 or 25, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 24 or 25; and

20 a VL domain comprising the amino acid sequence of SEQ ID NO: 26, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ ID NO: 26, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 26.

In some embodiments, the anti-TCR β V antibody molecule, *e.g.*, anti-TCR β V12 antibody molecule comprises:

30 a VH domain comprising the amino acid sequence of SEQ ID NO: 24 or 25, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ ID NO: 24 or 25, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 24 or 25; and

a VL domain comprising the amino acid sequence of SEQ ID NO: 27, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ ID NO: 27, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 27.

In some embodiments, the anti-TCR β V antibody molecule, *e.g.*, anti-TCR β V12 antibody molecule comprises:

a VH domain comprising the amino acid sequence of SEQ ID NO: 24 or 25, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence
5 SEQ ID NO: 24 or 25, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 24 or 25; and

a VL domain comprising the amino acid sequence of SEQ ID NO: 28, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ
10 ID NO: 28, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 28.

In some embodiments, the anti-TCR β V antibody molecule, *e.g.*, anti-TCR β V12 antibody molecule comprises:

a VH domain comprising the amino acid sequence of SEQ ID NO: 24 or 25, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence
15 SEQ ID NO: 24 or 25, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 24 or 25; and

a VL domain comprising the amino acid sequence of SEQ ID NO: 29, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ
20 ID NO: 29, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 29.

In some embodiments, the anti-TCR β V antibody molecule, *e.g.*, anti-TCR β V12 antibody molecule comprises:

a VH domain comprising the amino acid sequence of SEQ ID NO: 24 or 25, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence
25 SEQ ID NO: 24 or 25, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 24 or 25; and

a VL domain comprising the amino acid sequence of SEQ ID NO: 30, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ
30 ID NO: 30, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 30.

In some embodiments, the anti-TCR β V antibody molecule, *e.g.*, anti-TCR β V12 antibody molecule comprises:

a VH domain comprising the amino acid sequence of SEQ ID NO: 25 or 23, an amino
35 acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence
SEQ

ID NO: 25 or 23, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 25 or 23; and

5 a VL domain comprising the amino acid sequence of SEQ ID NO: 26, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ ID NO: 26, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 26.

In some embodiments, the anti-TCR β V antibody molecule, *e.g.*, anti-TCR β V12 antibody molecule comprises:

10 a VH domain comprising the amino acid sequence of SEQ ID NO: 25 or 23, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ ID NO: 25 or 23, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 25 or 23; and

15 a VL domain comprising the amino acid sequence of SEQ ID NO: 27, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ ID NO: 27, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 27.

In some embodiments, the anti-TCR β V antibody molecule, *e.g.*, anti-TCR β V12 antibody molecule comprises:

20 a VH domain comprising the amino acid sequence of SEQ ID NO: 25 or 23, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ ID NO: 25 or 23, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 25 or 23; and

25 a VL domain comprising the amino acid sequence of SEQ ID NO: 28, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ ID NO: 28, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 28.

In some embodiments, the anti-TCR β V antibody molecule, *e.g.*, anti-TCR β V12 antibody molecule comprises:

30 a VH domain comprising the amino acid sequence of SEQ ID NO: 25 or 23, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ ID NO: 25 or 23, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 25 or 23; and

a VL domain comprising the amino acid sequence of SEQ ID NO: 29, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ

ID NO: 29, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 29.

In some embodiments, the anti-TCR β V antibody molecule, *e.g.*, anti-TCR β V12 antibody molecule comprises:

5 a VH domain comprising the amino acid sequence of SEQ ID NO: 25 or 23, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ ID NO: 25 or 23, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 25 or 23; and

 a VL domain comprising the amino acid sequence of SEQ ID NO: 30, an amino acid
10 sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ ID NO: 30, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 30.

In some embodiments, the anti-TCR β V antibody molecule, *e.g.*, anti-TCR β V12 antibody molecule is a full antibody or fragment thereof (*e.g.*, a Fab, F(ab')₂, Fv, or a single chain Fv fragment (scFv)). In embodiments, the anti-TCR β V antibody molecule, *e.g.*, anti-TCR β V6 (*e.g.*, anti-TCR β V6-5*01) antibody molecule is a monoclonal antibody or an antibody with single specificity. In some embodiments, the anti-TCR β V antibody molecule, *e.g.*, anti-TCR β V12 antibody molecule, can also be a humanized, chimeric, camelid, shark, or an *in vitro*-generated antibody molecule. In some embodiments, the anti-TCR β V antibody
15 molecule, *e.g.*, anti-TCR β V12 antibody molecule is a humanized antibody molecule. The heavy and light chains of the anti-TCR β V antibody molecule, *e.g.*, anti-TCR β V12 antibody molecule can be full-length (*e.g.*, an antibody can include at least one, and preferably two, complete heavy chains, and at least one, and preferably two, complete light chains) or can include an antigen-binding fragment (*e.g.*, a Fab, F(ab')₂, Fv, a single chain Fv fragment, a single domain antibody,
20 a diabody (dAb), a bivalent antibody, or bispecific antibody or fragment thereof, a single domain variant thereof, or a camelid antibody).

In some embodiments, the anti-TCR β V antibody molecule, *e.g.*, anti-TCR β V12 antibody molecule is in the form of a multispecific molecule, *e.g.*, a bispecific molecule, *e.g.*, as described herein.

30 In some embodiments, the anti-TCR β V antibody molecule, *e.g.*, anti-TCR β V12 antibody molecule has a heavy chain constant region (Fc) chosen from, *e.g.*, the heavy chain constant regions of IgG1, IgG2, IgG3, IgG4, IgM, IgA1, IgA2, IgD, and IgE. In some embodiments, the Fc region is chosen from the heavy chain constant regions of IgG1, IgG2, IgG3, and IgG4. In some embodiments, the Fc region is chosen from the heavy chain constant

		YISSGSSTIYYADTLKGRFTISRDN AK NSLYLQMNSLRAEDTAVYYCARRGE GAMDYWGQGTTVTVSS
SEQ ID NO: 31	DNA VH	GAGGTGCAGCTGGTTGAATCTGGC GGAGGATTGGTTCAGCCTGGCGGC TCTCTGAGACTGTCTTGTGCCGCTT CTGGCTTCACCTTCTCCAACCTTCGG CATGCACTGGGTCCGACAGGCCCC TGGAAAAGGACTGGAATGGGTGTC CTACATCTCCTCCGGCTCCTCCACC ATCTACTACGCTGACACCCTGAAG GGCAGATTCACCATCTCTCGGGAC AACGCCAAGAAGTCCCTGTACCTG CAGATGAACAGCCTGAGAGCCGA GGACACCGCCGTGTACTACTGTGC TAGAAGAGGCGAGGGCGCCATGG ATTATTGGGGCCAGGGAACACAG TGACCGTGTCTAGC
Antibody B-H.1B HC-2		
SEQ ID NO: 17	HC CDR1 (Combined)	GFTFSNFGMH
SEQ ID NO: 18	HC CDR2 (Combined)	YISSGSSTIYYADTLKG
SEQ ID NO: 19	HC CDR3 (Combined)	RGEGAMDY
SEQ ID NO: 25	VH	EVQLVESGGGLVQPGGSLRLSCAAS GFTFSNFGMHWVRQAPGKGLEWVS YISSGSSTIYYADTLKGRFTISRDN SK NTLYLQMNSLRAEDTAVYYCARRG EGAMDYWGQGTTVTVSS
SEQ ID NO: 32	DNA VH	GAGGTGCAGCTGGTTGAATCTGGC GGAGGATTGGTTCAGCCTGGCGGC TCTCTGAGACTGTCTTGTGCCGCTT CTGGCTTCACCTTCTCCAACCTTCGG CATGCACTGGGTCCGACAGGCCCC TGGAAAAGGACTGGAATGGGTGTC CTACATCTCCTCCGGCTCCTCCACC ATCTACTACGCTGACACCCTGAAG GGCAGATTCACCATCAGCCGGGAC AACTCCAAGAACACCCTGTACCTG CAGATGAACTCCCTGAGAGCCGAG GACACCGCCGTGTACTACTGTGCT AGAAGAGGCGAGGGCGCCATGGA TTATTGGGGCCAGGGAACACAGT GACCGTGTCTAGC
Antibody B-H.1C HC-3		
SEQ ID NO: 17	HC CDR1 (Combined)	GFTFSNFGMH
SEQ ID NO: 18	HC CDR2 (Combined)	YISSGSSTIYYADTLKG
SEQ ID NO: 19	HC CDR3 (Combined)	RGEGAMDY
SEQ ID NO: 23	VH	QVQLVESGGGVVQPGSRSLRLSCAAS GFTFSNFGMHWVRQAPGKGLEWVA YISSGSSTIYYADTLKGRFTISRDN SK NTLYLQMNSLRAEDTAVYYCARRG EGAMDYWGQGTTVTVSS

		YVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVCTLP PSREEMTKNQVSLTSCAVKGFP SDIAVEWESNGQPENNYKTT PPVLDSDGSFFLVSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQK SLSLSPGKGGGSGGGGSGGLND IFEAQKIEWHE
SEQ ID NO: 3642	scFv	EVQLVESGGGLVQPGGSLRLSCAAS GFTFSNFGMHWVRQAPGKGLEWVS YISSGSSTIYYADTLKGRFTISR DNSKNTLYLQMNSLRAEDTAVYYC ARRGEGAMDYWGQGTFTVTVSSG GGGSGGGGSGGGGSDNQLTQSPS FLSASVGDRVTITCRASSSVNYIY WYQKQPGKAPKLLIYYTSNLAPG VPSRFGSGSGNEYTLTISSLQPE DFATYYCQQTSSPFTFGQGTKLEIK
Antibody B-H.2		
SEQ ID NO: 1338	scFv	EVQLVESGGGLVQPGGSLRLSCAAS GFTFSNFGMHWVRQAPGKGLEWVS YISSGSSTIYYADTLKGRFTISR DNSKNTLYLQMNSLRAEDTAVYYC ARRGEGAMDYWGQGTFTVTVSSG GGGSGGGGSGGGGSDNQLTQSPS SLSASVGDRVTITCRASSSVNYIY WYQKQPGKAPKLLIYYTSNLAPG VPSRFGSGSGNDYTLTISSLQPE DFATYYCQQTSSPFTFGQGTKLEIK
Antibody B-H.3		
SEQ ID NO: 1339	scFv	EVQLVESGGGLVQPGGSLRLSCAAS GFTFSNFGMHWVRQAPGKGLEWVS YISSGSSTIYYADTLKGRFTISR DNSKNTLYLQMNSLRAEDTAVYYC ARRGEGAMDYWGQGTFTVTVSSG GGGSGGGGSGGGGSSNELTQPPSV SVSPGQTARITCRASSSVNYIYWY QQKSGQAPVLVIYYTSNLAPGIP ERFSGSGSGNMYTLTISGAQVEDE ADYYCQQTSSPFTFGTGKVTVL
Antibody B-H.4		
SEQ ID NO: 1340	scFv	QVQLVESGGGVVQPGRSLRLSCAAS GFTFSNFGMHWVRQAPGKGLEWVA YISSGSSTIYYADTLKGRFTISR DNSKNTLYLQMNSLRAEDTAVYYC ARRGEGAMDYWGQGTFTVTVSSG GGGSGGGGSGGGGSDNQLTQSPS FLSASVGDRVTITCRASSSVNYIY WYQKQPGKAPKLLIYYTSNLAPG VPSRFGSGSGNEYTLTISSLQPE DFATYYCQQTSSPFTFGQGTKLEIK

IMMU 222 binds human TCR β V 6-5, TCR β V 6-6, or TCR β V 6-9 (TCR β V13.1 per old nomenclature). REA1062 binds human TCR β V 5-1). JOVI-3 binds human TCR β V 28 (TCR β V3.1 per old nomenclature). IMMU546 binds human TCR β V 2.

MPB2D5 (murine), also referred to here as BJ1188, BJ1190 and REA654; or Antibody G		
Binds to human TCRVβ 20-1		
SEQ ID NO: 1102	HC CDR1 (Kabat)	SAYMH
SEQ ID NO: 1103	HC CDR2 (Kabat)	RIDPATGKTKYAPKFQA
SEQ ID NO: 1104	HC CDR3 (Kabat)	SLNWDYGLDY
SEQ ID NO: 1105	HC CDR1 (Chothia)	GFNIKSA
SEQ ID NO: 1106	HC CDR2 (Chothia)	DPATGK
SEQ ID NO: 1104	HC CDR3 (Chothia)	SLNWDYGLDY
SEQ ID NO: 3640	HC CDR1 (Combined)	GFNIKSAYMH
SEQ ID NO: 1103	HC CDR2 (Combined)	RIDPATGKTKYAPKFQA
SEQ ID NO: 1104	HC CDR3 (Combined)	SLNWDYGLDY
SEQ ID NO: 1107	LC CDR1 (Kabat)	RASKSVSILGTHLIH
SEQ ID NO: 1108	LC CDR2 (Kabat)	AASNLES
SEQ ID NO: 1109	LC CDR3 (Kabat)	QQSIEDPWT
SEQ ID NO: 1110	LC CDR1 (Chothia)	SKSVSILGTHL
SEQ ID NO: 1108	LC CDR2 (Chothia)	AASNLES
SEQ ID NO: 1109	LC CDR3 (Chothia)	QQSIEDPWT
SEQ ID NO: 1107	LC CDR1 (Combined)	RASKSVSILGTHLIH
SEQ ID NO: 1108	LC CDR2 (Combined)	AASNLES
SEQ ID NO: 1109	LC CDR3(Combined)	QQSIEDPWT

		FSGSGSETDFTLTISRLEPEDFAVYFCQQSIEDP FGGGTKVEIK
CAS1.1.3 (murine) also referred to herein as BJ1460; or Antibody H Binds to human TCRVβ 27		
SEQ ID NO: 1120	HC CDR1 (Kabat)	DTYMY
SEQ ID NO: 1121	HC CDR2 (Kabat)	RIDPANGNTKYDPKFQD
SEQ ID NO: 1122	HC CDR3 (Kabat)	GSYYYAMDY
SEQ ID NO: 1123	HC CDR1 (Chothia)	GFKTEDT
SEQ ID NO: 1124	HC CDR2 (Chothia)	DPANGN
SEQ ID NO: 1122	HC CDR3 (Chothia)	GSYYYAMDY
SEQ ID NO: 1125	HC CDR1 (Combined)	GFKTEDTYMY
SEQ ID NO: 1121	HC CDR2 (Combined)	RIDPANGNTKYDPKFQD
SEQ ID NO: 1122	HC CDR3(Combined)	GSYYYAMDY
SEQ ID NO: 1126	LC CDR1 (Kabat)	RASESVDSYGNSFMH
SEQ ID NO: 1127	LC CDR2 (Kabat)	RASNLES
SEQ ID NO: 1128	LC CDR3 (Kabat)	QQSNEDPYT
SEQ ID NO: 3641	LC CDR1 (Chothia)	SESVDSYGNSF
SEQ ID NO: 1127	LC CDR2 (Chothia)	RASNLES
SEQ ID NO: 1128	LC CDR3 (Chothia)	QQSNEDPYT
SEQ ID NO: 1126	LC CDR1 (Combined)	RASESVDSYGNSFMH
SEQ ID NO: 1127	LC CDR2 (Combined)	RASNLES
SEQ ID NO: 1128	LC CDR3(Combined)	QQSNEDPYT
SEQ ID NO: 1129	VL	DIVLTQSPASLAVSLGQRATISCRASESVDSYGN SFMHWYQQKPGQPPKLLIYRASNLESGIPARFS GSGSRTDFTLTINPVEADDVATYYCQQS

	CDR3(Combined)	
SEQ ID NO: 1168	LC CDR1 (Kabat)	SASSSVSYMH
SEQ ID NO: 1169	LC CDR2 (Kabat)	EISKLAS
SEQ ID NO: 1170	LC CDR3 (Kabat)	QQWNYPLLT
SEQ ID NO: 1297	LC CDR1 (Chothia)	SSSVSY
SEQ ID NO: 1169	LC CDR2 (Chothia)	EISKLAS
SEQ ID NO: 1170	LC CDR3 (Chothia)	QQWNYPLLT
SEQ ID NO: 1168	LC CDR1 (Combined)	SASSSVSYMH
SEQ ID NO: 1169	LC CDR2 (Combined)	EISKLAS
SEQ ID NO: 1170	LC CDR3(Combined)	QQWNYPLLT
SEQ ID NO: 1171	VL	EIVLTQSPAITAASLGQKVTITCSASSSVSYMH WYQQKSGTSPKPWIYEISKLASGVPARFSGSG SGTSYSLTISSMEAEDAAIYYCQQWNYPLLT FAGATKLELK
SEQ ID NO: 1172	VH	EVQLQQSGPVLVKPGASVRMSCKASGYTFTD YNIHWVKQSHGRSLEWVGYNPYNGRTGYN QKFKAKATLTVDKSSSTAYMDLRSLTSEDSA VYYCARWDGSSYFDYWGQGTTTLTVSS
VH for REA1062 (humanized) also referred to as Antibody J-H Binds to human TCRVβ 5-1		
SEQ ID NO: 1173	VH - 1	QVQLVQSGAEVKKPGSSVKVSCASGYTFTD YNIHWVRQAPGQGLEWVGYNPYNGRTGYN QKFKARATLTVDKSTSTAYMELSSLRSEDTA VYYCARWDGSSYFDYWGQGTTTVTVSS
SEQ ID NO: 1174	VH - 2	QVQLVQSGAEVKKPGASVKVSCASGYTFT DYNHWVRQAPGQGLEWVGYNPYNGRTGY NQKFKARATLTVDKSTSTAYMELRSLRSDDM AVYYCARWDGSSYFDYWGQGTTTVTVSS
SEQ ID NO: 1175	VH - 3	QVQLVQSGAEVKKPGASVKVSCASGYTFT DYNHWVRQATGQGLEWVGYNPYNGRTGY NQKFKARATLTVNKSISTAYMELSSLRSEDTA

binds to TRVβ 11-2		
SEQ ID NO: 1283	VH-1	QVTLKESGPVLVKPTETLTLTCTVSGFSLTN YGVHWVRQPPGKALEWLGVIWSDGSTDYD TAFISRLTISKDNSKSQVVLMTNMDPVDTA TYYCARRAVVADFDYWGQGTTVTVSS
SEQ ID NO: 1284	VH-2	QVQLQESGPGLVKPSGTLSTCAVSGFSLTN YGVHWVRQPPGKGLEWLGVIWSDGSTDYD TAFISRLTISKDNSKSQVSLKLSSVTAADTAV YYCARRAVVADFDYWGQGTTVTVSS
SEQ ID NO: 1285	VH-3	QVQLQQSGPGLVKPSQTLSTCAVSGFSLTN YGVHWVRQSPSRGLEWLGVIWSDGSTDYDT AFISRLTINKDNSKSQVSLQLNSVTPEDTAVY YCARRAVVADFDYWGQGTTVTVSS
SEQ ID NO: 1286	VH-4	EVQLVESGGGLVQPGPSLRLSCTVSGFSLTN YGVHWVRQAPGKGLEWLGVIWSDGSTDYD TAFISRLTISKDNSKSIVYLMNSLKTEDTAV YYCARRAVVADFDYWGQGTTVTVSS
SEQ ID NO: 1287	VH-5	EVQLVQSGAEVKKPGESLRISCKVSGFSLTN YGVHWVRQMPGKGLEWLGVIWSDGSTDYD TAFISQLTISKDNSISTVYLQWSSLKASDTAM YYCARRAVVADFDYWGQGTTVTVSS
MR5-2 (murine), Binds to human TCRVβ 13-2		
SEQ ID NO: 1376	SCFV (VH + VL)	QVQLQQSGTELMKPGASVKISCKASGYTFSN YWIEWIKQRPBGHGLEWVGEILPGAGPTNYN EKFKGKATFTADSSSNTAYMQLSSLTSEDSA VYYCARTDYDYDWFAYWGQGLTVTSAG GGGSGGGSGGGSGGGSGDIVMSQSPSSL AVSVGEKVTMSCKSSQSLLYSGNQKNYLAW YQQKPGQSPKLLIYWASTRESGVPDRFTGSG SGTDFTLTINSVKAEDLTVYYCQQYGYPRP FGGGTKVEIK

Anti-TCRV β antibody effector function and Fc variants

In some embodiments, an anti-TCRV β antibody disclosed herein comprises an Fc region, e.g., as described herein. In some embodiments, the Fc region is a wildtype Fc region, e.g., a wildtype human Fc region. In some embodiments, the Fc region comprises a variant, e.g., an Fc region comprising an addition, substitution, or deletion of at least one amino acid residue in the Fc region which results in, e.g., reduced or ablated affinity for at least one Fc receptor.

CLAIMS

WHAT IS CLAIMED IS:

1. A molecule comprising an antigen binding domain that binds to T cell receptor beta variable region (TCR β V), wherein the antigen binding domain comprises:

- (i) a heavy chain variable region (VH) comprising a heavy chain complementarity determining region 1 (HC CDR1), a heavy chain complementarity determining region 2 (HC CDR2), and a heavy chain complementarity determining region 3 (HC CDR3) of SEQ ID NO: 1100, and a light chain variable region (VL) comprising a light chain complementarity determining region 1 (LC CDR1), a light chain complementarity determining region 2 (LC CDR2), and a light chain complementarity determining region 3 (LC CDR3) of SEQ ID NO: 1101;
- (ii) a VH comprising a HC CDR1, a HC CDR2, and a HC CDR3 of SEQ ID NO: 1346, and a VL comprising a LC CDR1, a LC CDR2, and a LC CDR3 of SEQ ID NO: 1347 or SEQ ID NO: 1349;
- (iii) a VH comprising a HC CDR1, a HC CDR2, and a HC CDR3 of SEQ ID NO: 1348, and a VL comprising a LC CDR1, a LC CDR2, and a LC CDR3 of SEQ ID NO: 1349;
- (iv) a VH comprising a HC CDR1, a HC CDR2, and a HC CDR3 of SEQ ID NO: 1350, and a VL comprising a LC CDR1, a LC CDR2, and a LC CDR3 of SEQ ID NO: 1349, SEQ ID NO: 1351, SEQ ID NO: 1353, SEQ ID NO: 1365, SEQ ID NO: 1367, or SEQ ID NO: 1369;
- (v) a VH comprising a HC CDR1, a HC CDR2, and a HC CDR3 of SEQ ID NO: 1356, and a VL comprising a LC CDR1, a LC CDR2, and a LC CDR3 of SEQ ID NO: 1357;
- (vi) a VH comprising a HC CDR1, a HC CDR2, and a HC CDR3 of SEQ ID NO: 1360 or SEQ ID NO: 1362, and a VL comprising a LC CDR1, a LC CDR2, and a LC CDR3 of SEQ ID NO: 1361;
- (vii) a VH comprising a HC CDR1, a HC CDR2, and a HC CDR3 of SEQ ID NO: 1370, and a VL comprising a LC CDR1, a LC CDR2, and a LC CDR3 of SEQ ID NO: 1365, SEQ ID NO: 1367, or SEQ ID NO: 1369;
- (viii) a VH comprising a HC CDR1, a HC CDR2, and a HC CDR3 of SEQ ID NO: 1112, SEQ ID NO: 1113, SEQ ID NO: 1114, SEQ ID NO: 1115, or SEQ ID NO: 1116, and a VL comprising a LC CDR1, a LC CDR2, and a LC CDR3 of SEQ ID NO: 1111;

- (ix) a VH comprising a HC CDR1, a HC CDR2, and a HC CDR3 of SEQ ID NO: 1310 or SEQ ID NO: 1311, and a VL comprising a LC CDR1, a LC CDR2, and a LC CDR3 of SEQ ID NO: 1313;
- (x) a VH comprising a HC CDR1, a HC CDR2, and a HC CDR3 of SEQ ID NO: 1312, and a VL comprising a LC CDR1, a LC CDR2, and a LC CDR3 of SEQ ID NO: 1314; or
- (xi) a single chain variable fragment (scfv) comprising a HC CDR1, a HC CDR2, a HC CDR3, a LC CDR1, a LC CDR2, and a LC CDR3 of any one sequence selected from the group consisting of SEQ ID NOs: 1309, 1326-1337, and 110.

2. The molecule of claim 1, wherein the antigen binding domain comprises:

- (i) a VH comprising a HC CDR1 sequence, a HC CDR2 sequence, and a HC CDR3 sequence comprising the sequence of SEQ ID NO: 3, the sequence of SEQ ID NO: 4, and the sequence of SEQ ID NO: 5, respectively, and a VL comprising a LC CDR1 sequence, a LC CDR2 sequence, and a LC CDR3 sequence comprising the sequence of SEQ ID NO: 6, the sequence of SEQ ID NO: 7, and the sequence of SEQ ID NO: 8, respectively;
- (ii) a VH comprising a HC CDR1 sequence, a HC CDR2 sequence, and a HC CDR3 sequence comprising the sequence of SEQ ID NO: 45, the sequence of SEQ ID NO: 46, and the sequence of SEQ ID NO: 47, respectively, and a VL comprising a LC CDR1 sequence, a LC CDR2 sequence, and a LC CDR3 sequence comprising the sequence of SEQ ID NO: 51, the sequence of SEQ ID NO: 52, and the sequence of SEQ ID NO: 53, respectively;
- (iii) a VH comprising a HC CDR1 sequence, a HC CDR2 sequence, and a HC CDR3 sequence comprising the sequence of SEQ ID NO: 48, the sequence of SEQ ID NO: 49, and the sequence of SEQ ID NO: 50, respectively, and a VL comprising a LC CDR1 sequence, a LC CDR2 sequence, and a LC CDR3 sequence comprising the sequence of SEQ ID NO: 54, the sequence of SEQ ID NO: 55, and the sequence of SEQ ID NO: 56, respectively;
- (iv) a VH comprising a HC CDR1 sequence, a HC CDR2 sequence, and a HC CDR3 sequence comprising the sequence of SEQ ID NO: 3640, the sequence of SEQ ID NO: 1103, and the sequence of SEQ ID NO: 1104, respectively, and a VL comprising a LC CDR1 sequence, a LC CDR2 sequence, and a LC CDR3 sequence comprising the sequence of SEQ ID NO: 1107, the sequence of SEQ ID NO: 1108, and the sequence of SEQ ID NO: 1109, respectively;
- (v) a VH comprising a HC CDR1 sequence, a HC CDR2 sequence, and a HC CDR3

sequence comprising the sequence of SEQ ID NO: 1102, the sequence of SEQ ID NO: 1103, and the sequence of SEQ ID NO: 1104, respectively, and a VL comprising a LC CDR1 sequence, a LC CDR2 sequence, and a LC CDR3 sequence comprising the sequence of SEQ ID NO: 1107, the sequence of SEQ ID NO: 1108, and the sequence of SEQ ID NO: 1109, respectively; or

(vi) a VH comprising a HC CDR1 sequence, a HC CDR2 sequence, and a HC CDR3 sequence comprising the sequence of SEQ ID NO: 1105, the sequence of SEQ ID NO: 1106, and the sequence of SEQ ID NO: 1104, respectively, and a VL comprising a LC CDR1 sequence, a LC CDR2 sequence, and a LC CDR3 sequence comprising the sequence of SEQ ID NO: 1110, the sequence of SEQ ID NO: 1108, and the sequence of SEQ ID NO: 1109, respectively.

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

(i) a VH comprising a sequence having at least 80% sequence identity to any one sequence selected from the group consisting of SEQ ID NOs: 1100, 1310, 1311, 1312, 1346, 1348, 1350, 1356, 1360, 1362, and 1370, and/or a VL comprising a sequence having at least 80% sequence identity to any one sequence selected from the group consisting of SEQ ID NOs: 1101, 1313, 1314, 1347, 1349, 1351, 1353, 1365, 1367, 1369, 1357, 1361, 1365, 1367, and 1369; or

(ii) a VH comprising a sequence having at least 80% sequence identity to any one sequence selected from the group consisting of SEQ ID NOs: 1112, 1113, 1114, 1115, and 1116, and/or a VL comprising a sequence having at least 80% sequence identity to the sequence of SEQ ID NO: 1111.

4. The molecule of any one of claims 1-3, wherein the antigen binding domain comprises:

(i) a VH comprising a sequence selected from the group consisting of SEQ ID NOs: 1100, 1310, 1311, 1312, 1346, 1348, 1350, 1356, 1360, 1362, and 1370, and/or a VL comprising a sequence selected from the group consisting of SEQ ID NOs: 1101, 1313, 1314, 1347, 1349, 1351, 1353, 1365, 1367, 1369, 1357, 1361, 1365, 1367, and 1369; or

(ii) a VH comprising a sequence selected from the group consisting of SEQ ID NOs: 1112, 1113, 1114, 1115, and 1116, and/or a VL comprising the sequence of SEQ ID NO: 1111.

5. The molecule of any one of claims 1-4, wherein the antigen binding domain comprises:

- (i) a VH and a VL comprising a sequence having at least 80% sequence identity to the sequence of SEQ ID NO: 1100, and a sequence having at least 80% sequence identity to the sequence of SEQ ID NO: 1101, respectively;
- (ii) a VH and a VL comprising a sequence having at least 80% sequence identity to the sequence of SEQ ID NO: 1346, and a sequence having at least 80% sequence identity to the sequence of SEQ ID NO: 1347 or SEQ ID NO: 1349, respectively;
- (iii) a VH and a VL comprising a sequence having at least 80% sequence identity to the sequence of SEQ ID NO: 1348, and a sequence having at least 80% sequence identity to the sequence of SEQ ID NO: 1349, respectively;
- (iv) a VH and a VL comprising a sequence having at least 80% sequence identity to the sequence of SEQ ID NO: 1350, and a sequence having at least 80% sequence identity to the sequence of SEQ ID NO: 1349, SEQ ID NO: 1351, SEQ ID NO: 1353, SEQ ID NO: 1365, SEQ ID NO: 1367, or SEQ ID NO: 1369, respectively;
- (v) a VH and a VL comprising a sequence having at least 80% sequence identity to the sequence of SEQ ID NO: 1356, and a sequence having at least 80% sequence identity to the sequence of SEQ ID NO: 1357, respectively;
- (vi) a VH and a VL comprising a sequence having at least 80% sequence identity to the sequence of SEQ ID NO: 1360 or SEQ ID NO: 1362, and a sequence having at least 80% sequence identity to the sequence of SEQ ID NO: 1361, respectively;
- (vii) a VH and a VL comprising a sequence having at least 80% sequence identity to the sequence of SEQ ID NO: 1370, and a sequence having at least 80% sequence identity to the sequence of SEQ ID NO: 1365, SEQ ID NO: 1367, SEQ ID NO: 1369, respectively;
- (viii) a VH and a VL comprising a sequence having at least 80% sequence identity to the sequence of SEQ ID NO: 1310 or SEQ ID NO: 1311, and a sequence having at least 80% sequence identity to the sequence of SEQ ID NO: 1313, respectively;
- (ix) a VH and a VL comprising a sequence having at least 80% sequence identity to the sequence of SEQ ID NO: 1312, and a sequence having at least 80% sequence identity to the sequence of SEQ ID NO: 1314, respectively; or
- (x) a VH and a VL comprising a sequence having at least 80% sequence identity to the sequence of SEQ ID NO: 1112, SEQ ID NO: 1113, SEQ ID NO: 1114, SEQ ID NO: 1115, or SEQ ID NO: 1116, and a sequence having at least 80% sequence identity to the sequence of SEQ ID NO: 1111, respectively.

6. The molecule of any one of claims 1-5, wherein the antigen binding domain comprises:
- (i) a VH and a VL comprising the sequence of SEQ ID NO: 1100, and the sequence of SEQ ID NO: 1101, respectively;
 - (ii) a VH and a VL comprising the sequence of SEQ ID NO: 1346, and the sequence of SEQ ID NO: 1347 or SEQ ID NO: 1349, respectively;
 - (iii) a VH and a VL comprising the sequence of SEQ ID NO: 1348, and the sequence of SEQ ID NO: 1349, respectively;
 - (iv) a VH and a VL comprising the sequence of SEQ ID NO: 1350, and the sequence of SEQ ID NO: 1349, SEQ ID NO: 1351, SEQ ID NO: 1353, SEQ ID NO: 1365, SEQ ID NO: 1367, or SEQ ID NO: 1369, respectively;
 - (v) a VH and a VL comprising the sequence of SEQ ID NO: 1356, and the sequence of SEQ ID NO: 1357, respectively;
 - (vi) a VH and a VL comprising the sequence of SEQ ID NO: 1360 or SEQ ID NO: 1362, and the sequence of SEQ ID NO: 1361, respectively;
 - (vii) a VH and a VL comprising the sequence of SEQ ID NO: 1370, and the sequence of SEQ ID NO: 1365, SEQ ID NO: 1367, SEQ ID NO: 1369, respectively;
 - (viii) a VH and a VL comprising the sequence of SEQ ID NO: 1310 or SEQ ID NO: 1311, and the sequence of SEQ ID NO: 1313, respectively;
 - (ix) a VH and a VL comprising the sequence of SEQ ID NO: 1312, and the sequence of SEQ ID NO: 1314, respectively; or
 - (x) a VH and a VL comprising the sequence of SEQ ID NO: 1112, SEQ ID NO: 1113, SEQ ID NO: 1114, SEQ ID NO: 1115, or SEQ ID NO: 1116, and the sequence of SEQ ID NO: 1111, respectively.
7. The molecule of claim 1, wherein the antigen binding domain comprises a sequence having at least 80% sequence identity to any one sequence selected from the group consisting of SEQ ID NOs: 1309, 1326-1337, and 110.
8. The molecule of claim 1 or 7, wherein the antigen binding domain comprises a sequence selected from the group consisting of SEQ ID NOs: 1309, 1326-1337, and 110.
9. The molecule of any one of claims 1-8, wherein the molecule further comprises:
- (i) one or more heavy chain constant regions selected from the group consisting of IgG1 heavy chain constant region or fragment thereof, IgG2 heavy chain constant region or

fragment thereof, IgG3 heavy chain constant region or fragment thereof, IgGA1 heavy chain constant region or fragment thereof, IgGA2 heavy chain constant region or fragment thereof, IgG4 heavy chain constant region or fragment thereof, IgJ heavy chain constant region or fragment thereof, IgM heavy chain constant region or fragment thereof, IgD heavy chain constant region or fragment thereof, and IgE heavy chain constant region or fragment thereof;

(ii) a kappa light chain constant region or fragment thereof, or a lambda light chain constant region or fragment thereof; or

(iii) a combination thereof.

10. The molecule of any one of claims 1-9, wherein the molecule is a multispecific molecule that further comprises one or more of a tumor-targeting moiety, a cytokine molecule, a stromal modifying moiety, or an immune cell engager, and

optionally, wherein the immune cell engager is selected from the group consisting of a T cell engager, an NK cell engager, a B cell engager, a dendritic cell engager, a macrophage cell engager, and any combination thereof.

11. The molecule of claim 10, wherein the molecule comprises the following configuration:

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

wherein:

(A) the dimerization module comprises immunoglobulin constant domains;

(B) A, B, C, and D are independently (i) absent; (ii) the antigen binding domain; (iii) the tumor targeting moiety, (iv) the cytokine molecule; (v) the stromal modifying moiety; or (vi) the immune cell engager; and

wherein at least one, two, or three of A, B, C, and D comprises the antigen binding domain.

12. The molecule of claim 10 or 11, wherein the cytokine molecule is selected from the group consisting of 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, and any combination thereof.

13. The molecule of any one of claims 10-12, wherein the tumor-targeting moiety binds to a cancer antigen, wherein:

(i) the cancer antigen is present on a hematological cancer, a solid tumor, a metastatic cancer, a soft tissue tumor, a metastatic lesion, or any combination thereof;

(ii) the cancer antigen is a tumor antigen, a stromal antigen, or a hematological antigen; or

(iii) the cancer antigen is selected from the group consisting of BCMA, CD19, CD20, CD22, FcRH5, PDL1, CD47, ganglioside 2 (GD2), prostate stem cell antigen (PSCA), prostate specific membrane antigen (PMSA), prostate-specific antigen (PSA), carcinoembryonic antigen (CEA), Ron Kinase, c-Met, Immature laminin receptor, TAG-72, BING-4, Calcium-activated chloride channel 2, Cyclin-B1, 9D7, Ep-CAM, EphA3, Her2/neu, Telomerase, SAP-1, Survivin, NY-ESO-1/LAGE-1, PRAME, SSX-2, Melan-A/MART-1, Gp100/pmel17, Tyrosinase, MC1R, β -catenin, BRCA1/2, CDK4, CML66, Fibronectin, p53, Ras, TGF-B receptor, AFP, ETA, MAGE, CA-125, BAGE, GAGE, CDC27, α actinin-4, TRP1/gp75, TRP2, gangliosides, WT1, Epidermal growth factor receptor (EGFR), MART-2, MUC1, MUC2, MUM1, MUM2, MUM3, NA88-1, NPM, OA1, OGT, RCC, RU11, RU12, SAGE, TRG, TSTA, Folate receptor alpha, L1-CAM, CAIX, gpA33, GD3, GM2, VEGFR, Integrins, Carbohydrates, IGF1R, TRAILR1, TRAILR2, RANKL, FAP, TGF-beta, hyaluronic acid, collagen, tenascin C, and tenascin W.

14. The molecule of any one of claims 1-13, wherein the antigen binding domain is a full antibody or an antigen-binding fragment thereof, a bivalent antibody, a bispecific antibody, or a biparatopic antibody, and

optionally, wherein the antigen-binding fragment is a Fab, a F(ab')₂, a Fv, a single chain Fv (scFv), a single domain antibody, a diabody (dAb), a single domain antibody, or a camelid antibody.

15. The molecule of any one of claims 1-14, wherein binding of the molecule to the TCR β V region results in one, two, three or all of:

(i) reduced T cell proliferation kinetics;

(ii) target cell killing;

(iii) increased Natural Killer (NK) cell proliferation; or

(iv) expansion of a population of T cells having a memory-like phenotype,

relative to a non-TCR β V-binding T cell engager, optionally, wherein the non-TCR β V-binding T cell engager comprises an antibody that binds to a CD3 molecule or a TCR α (TCR α) molecule.

16. A recombinant polynucleotide comprising a sequence encoding the molecule of any one of claims 1-15.

17. A pharmaceutical composition comprising the molecule of any one of claims 1-15, and a pharmaceutically acceptable carrier, excipient, or stabilizer for use in therapy.

18. Use of a pharmaceutical composition comprising the molecule of any one of claims 1-15 in the manufacture of a medicament for treating cancer in a subject in need thereof,

wherein an effective amount of the molecule is to be administered to the subject.

19. The use of claim 18, wherein the administration of the effective amount of the molecule treats or reduces cytokine release syndrome (CRS) and/or neurotoxicity (NT) in the subject.

20. The use of claim 19, wherein the administration of the effective amount of the molecule results in a cytokine profile that differs from a cytokine profile induced by a non-TCR β V-binding T cell engager, and

optionally, wherein the non-TCR β V-binding T cell engager comprises an antibody that binds to a CD3 molecule or a TCR alpha (TCR α) molecule.

21. The use of claim 20, wherein the cytokine profile of the molecule comprises one, two, three, four, five, six, seven, or all of:

- (i) an increased level and/or activity of IL-2;
- (ii) a reduced level and/or activity of IL-1 β ;
- (iii) a reduced level and/or activity of IL-6;
- (iv) a reduced level and/or activity of TNF α ;
- (v) a reduced level and/or activity of IL-10;
- (vi) a delay in increased level and/or activity of IL-2;
- (vii) a delay in increased level and/or activity of IFN γ ; or
- (viii) an increased level and/or activity of IL-15;

relative to the cytokine profile of the non-TCR β V-binding T cell engager.

22. The use of any one of claims 18-21, wherein the cancer is a solid tumor or a hematological cancer.

23. The use of claim 22, wherein:

(i) the solid tumor is melanoma, pancreatic, optionally pancreatic adenocarcinoma, cancer, breast cancer, colorectal cancer, lung cancer, skin cancer, ovarian cancer, or liver cancer; or

(ii) the hematological cancer is a B-cell malignancy or T cell malignancy, wherein the B-cell malignancy or T cell malignancy is Hodgkin's lymphoma, Non-Hodgkin's lymphoma, hairy cell leukemia, acute myeloid leukemia (AML), chronic myeloid leukemia, myelodysplastic syndrome, multiple myeloma, or acute lymphocytic leukemia,

optionally, wherein the Non-Hodgkin's lymphoma is B cell lymphoma, diffuse large B cell lymphoma (DLBCL), follicular lymphoma, chronic lymphocytic leukemia (B-CLL), mantle cell lymphoma, marginal zone B-cell lymphoma, Burkitt lymphoma, or lymphoplasmacytic lymphoma.

24. Use of a composition comprising the molecule of any one of claims 1-15 in the manufacture of a medicament for modulating an immune response in a subject in need thereof,

optionally, wherein an effective amount of the molecule expands an immune cell population,
optionally, wherein the expansion occurs *in vivo* or *ex vivo*.