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(54) HETERODIMERIC TETRAVALENCY AND SPECIFICITY ANTIBODY COMPOSITIONS AND USES THEREOF

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A61K 39/395	(2006.01)

(52) **U.S. Cl.**

CPC ***C07K 16/468*** (2013.01); ***C07K 16/2809*** (2013.01); ***A61K 39/39558*** (2013.01); ***C07K 16/32*** (2013.01); ***A61P 35/00*** (2018.01); ***C07K 16/3084*** (2013.01)

(57) **ABSTRACT**

The present disclosure relates generally to immunoglobulin-related compositions (e.g., heterodimeric trivalent/tetravalent multispecific antibodies) that specifically bind to three or four distinct target antigens. The immunoglobulin-related compositions described herein are useful in methods for detecting and treating cancer in a subject in need thereof.

Specification includes a Sequence Listing.

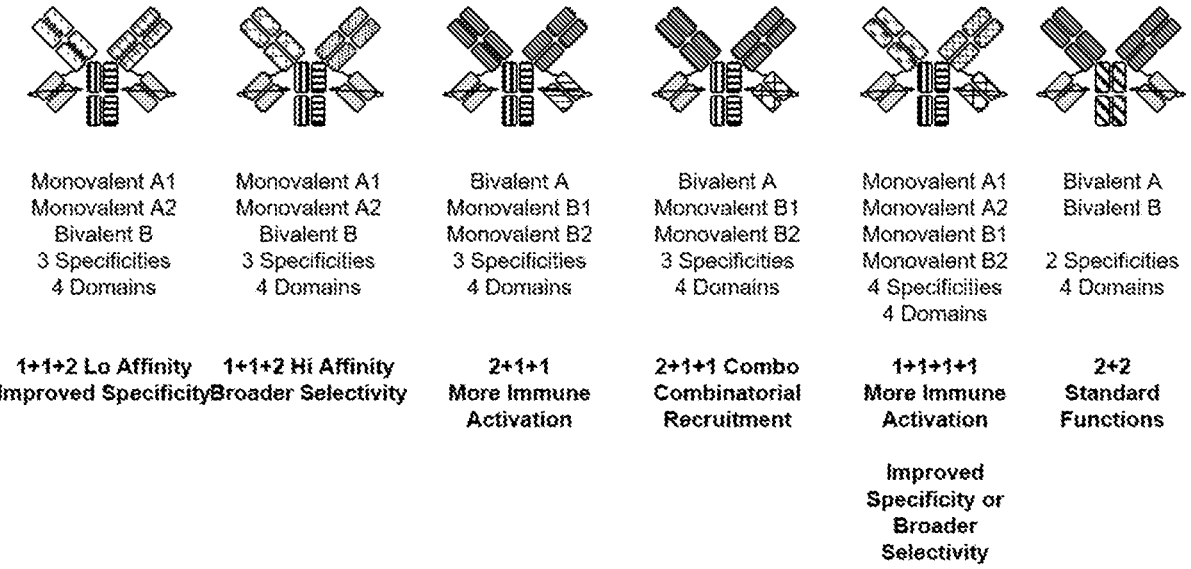


Figure 1a

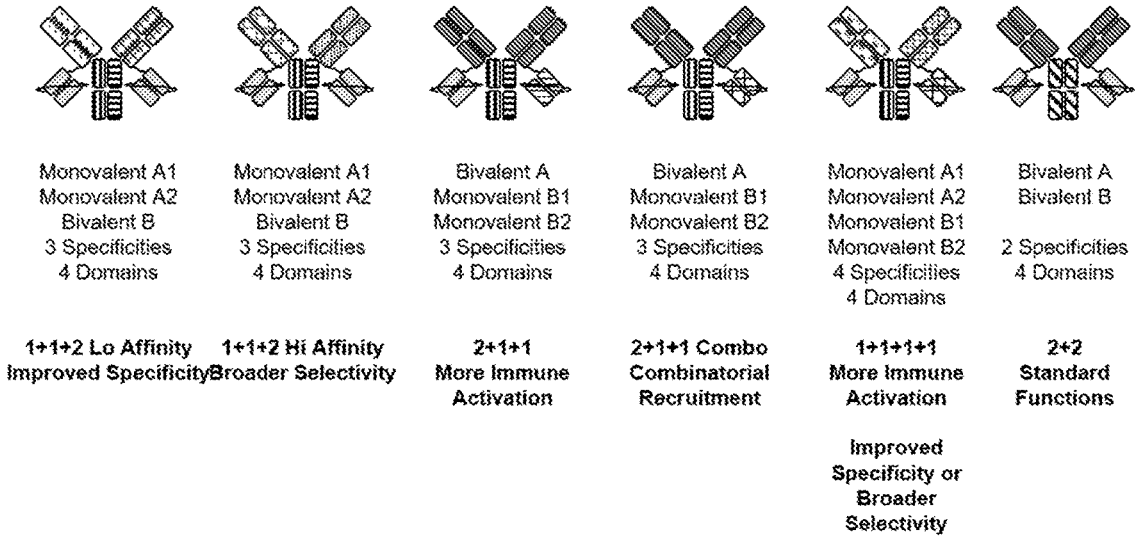


Figure 1b

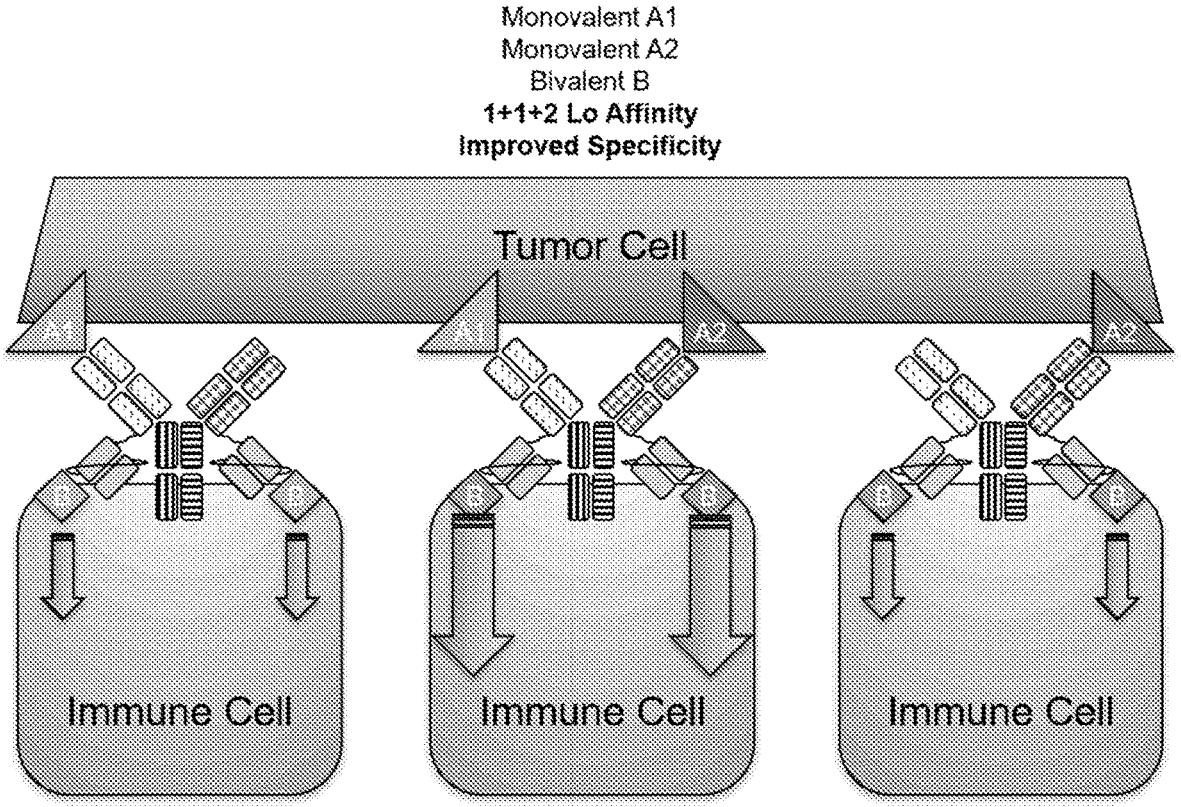


Figure 1c

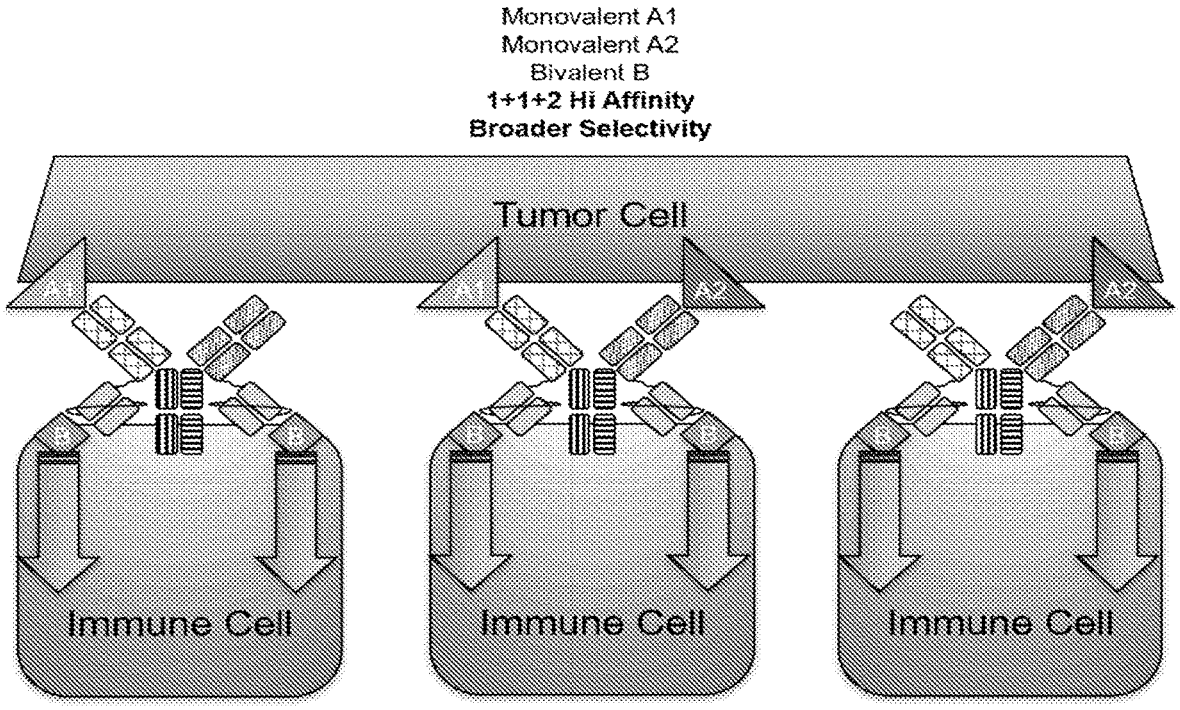

Monovalent A1
Monovalent A2
Bivalent B
1+1+2 Hi Affinity
Broader Selectivity
Tumor Cell
A1
A2
A2
B
B
Immune Cell
Immune Cell
Immune Cell

Figure 1d

Bivalent A
Monovalent B1
Monovalent B2
2+1+1
Better Immune Activation

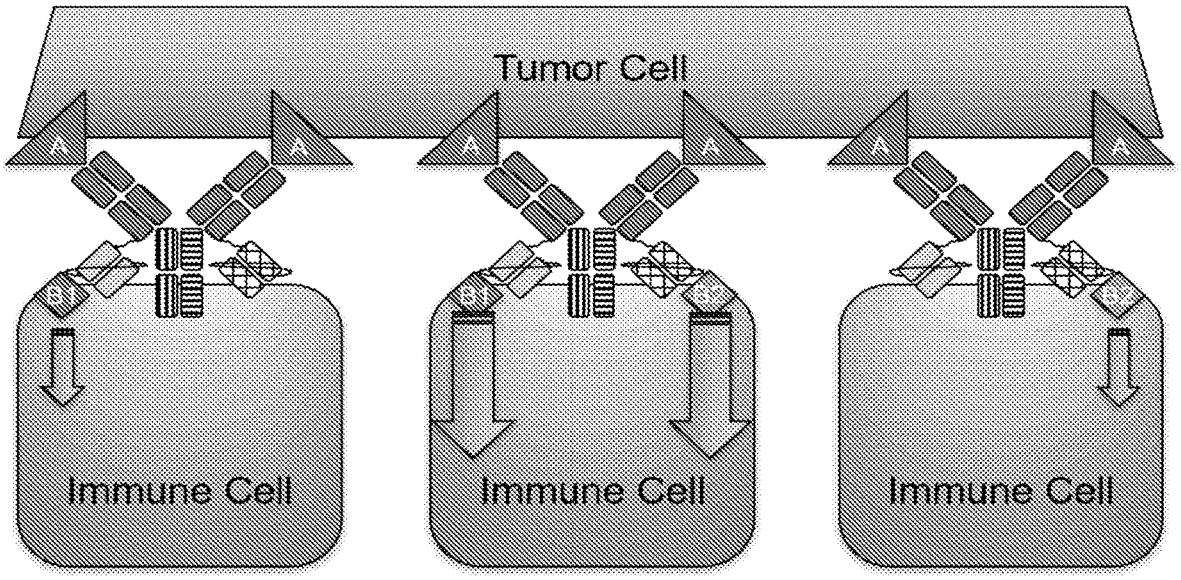


Figure 1e

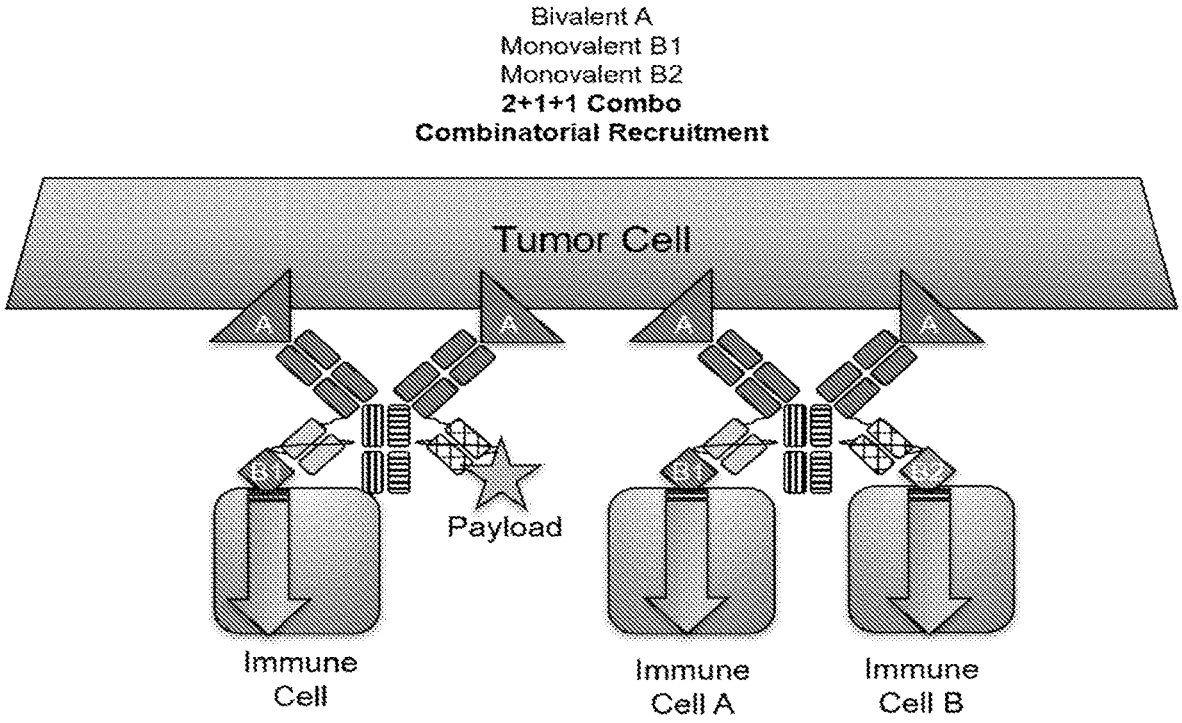

Bivalent A
Monovalent B1
Monovalent B2
2+1+1 Combo
Combinatorial Recruitment
Tumor Cell
A
A
A
A
B1
B1
B2
Payload
Immune Cell
Immune Cell A
Immune Cell B

Figure 1f

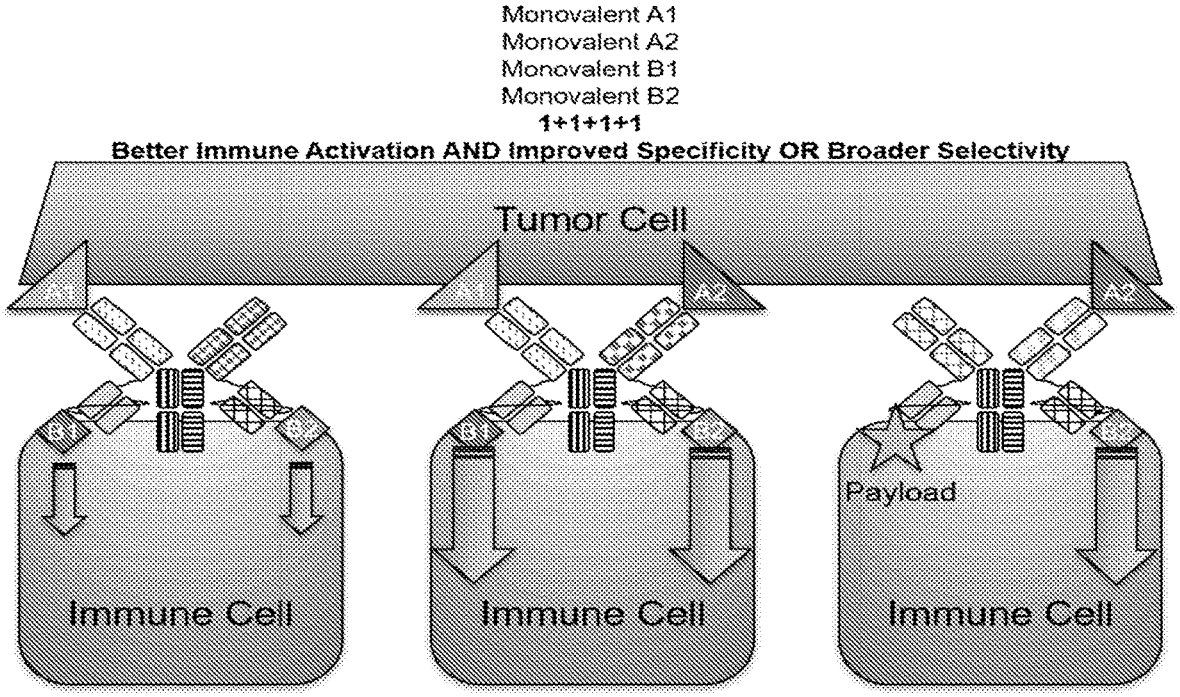

Monovalent A1
Monovalent A2
Monovalent B1
Monovalent B2
1+1+1+1
Better Immune Activation AND Improved Specificity OR Broader Selectivity
Tumor Cell
A1
A2
B1
B2
Payload
Immune Cell
Immune Cell
Immune Cell

Figure 2a

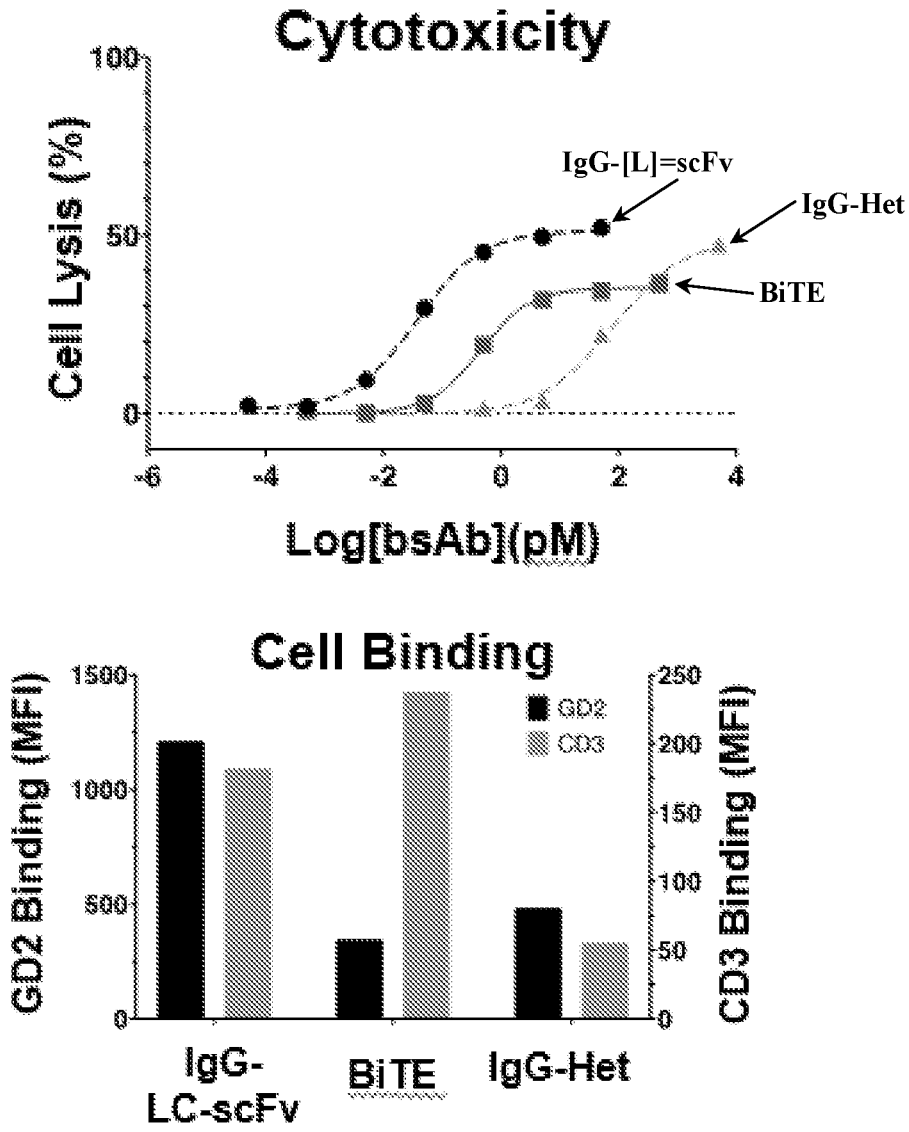

Cytotoxicity
Cell Lysis (%)
100
50
0
IgG-[L]=scFv
IgG-Het
BiTE
-6
-4
-2
0
2
4
Log[bsAb](pM)
Cell Binding
GD2 Binding (MFI)
1500
1000
500
0
GD2
CD3
250
200
150
100
50
0
CD3 Binding (MFI)
IgG-LC-scFv
BiTE
IgG-Het

Figure 2a (cont.)

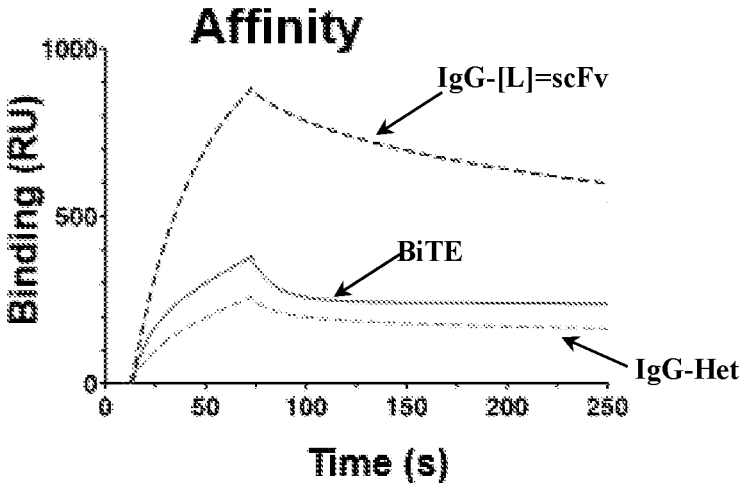


Figure 2a (cont.)

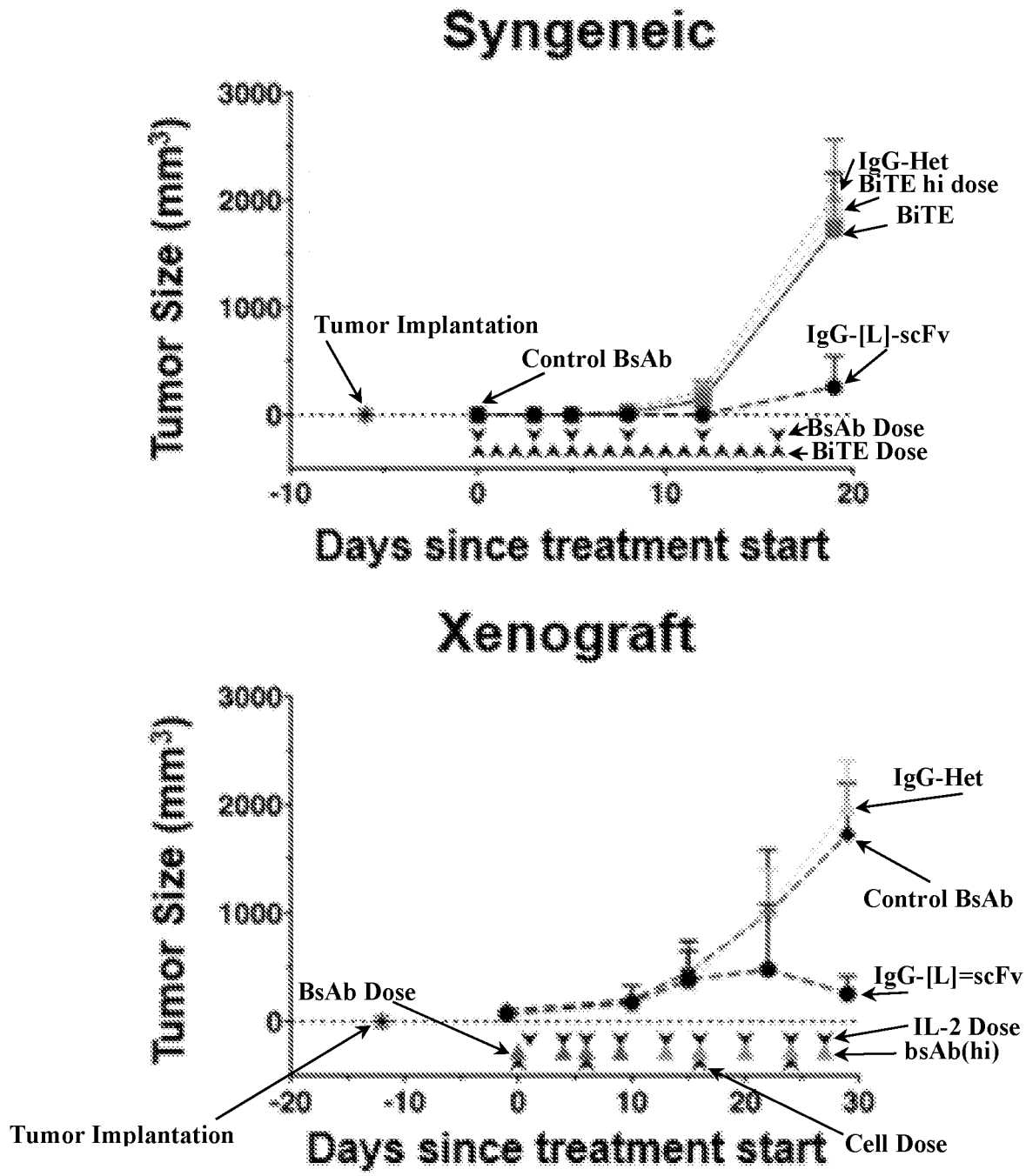


Figure 2b

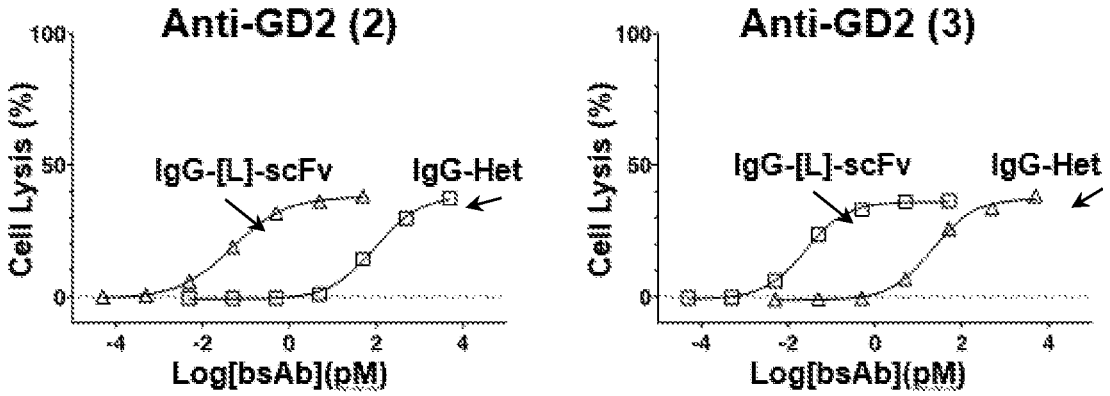

Anti-GD2 (2)
Cell Lysis (%)
100
50
0
IgG-[L]-scFv
IgG-Het
-4
-2
0
2
4
Log[bsAb](pM)
Anti-GD2 (3)
Cell Lysis (%)
100
50
0
IgG-[L]-scFv
IgG-Het
-4
-2
0
2
4
Log[bsAb](pM)

Figure 3

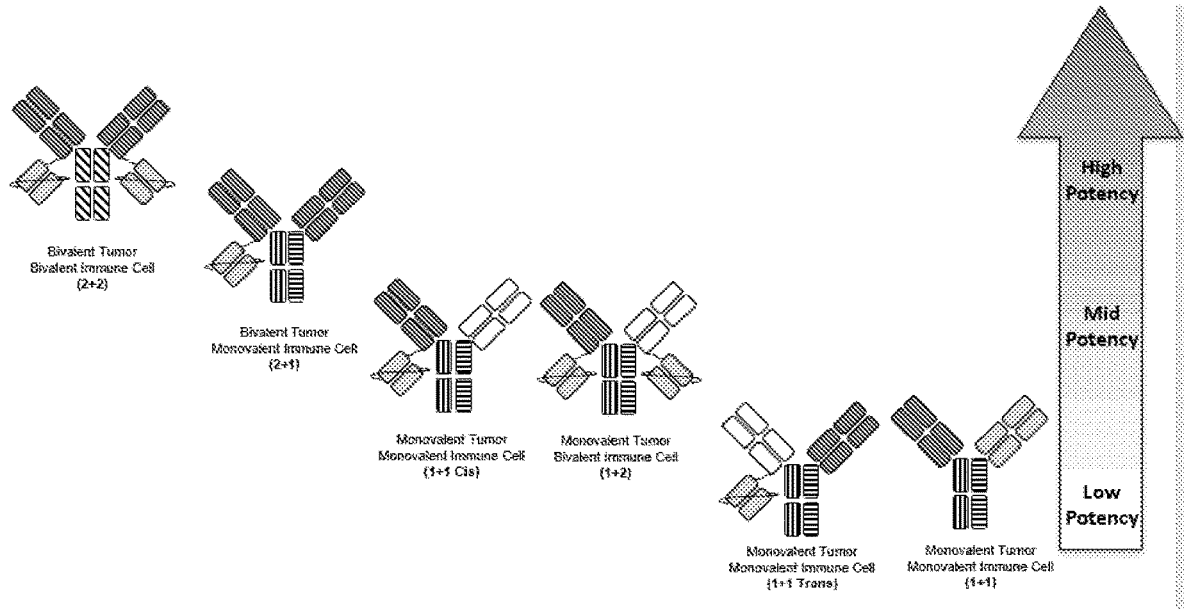

Bivalent Tumor
Bivalent Immune Cell
(2+2)
Bivalent Tumor
Monovalent Immune Cell
(2+1)
Monovalent Tumor
Monovalent Immune Cell
(1+1 Cis)
Monovalent Tumor
Bivalent Immune Cell
(1+2)
Monovalent Tumor
Monovalent Immune Cell
(1+1 Trans)
Monovalent Tumor
Monovalent Immune Cell
(1+1)
High Potency
Mid Potency
Low Potency

Figure 4

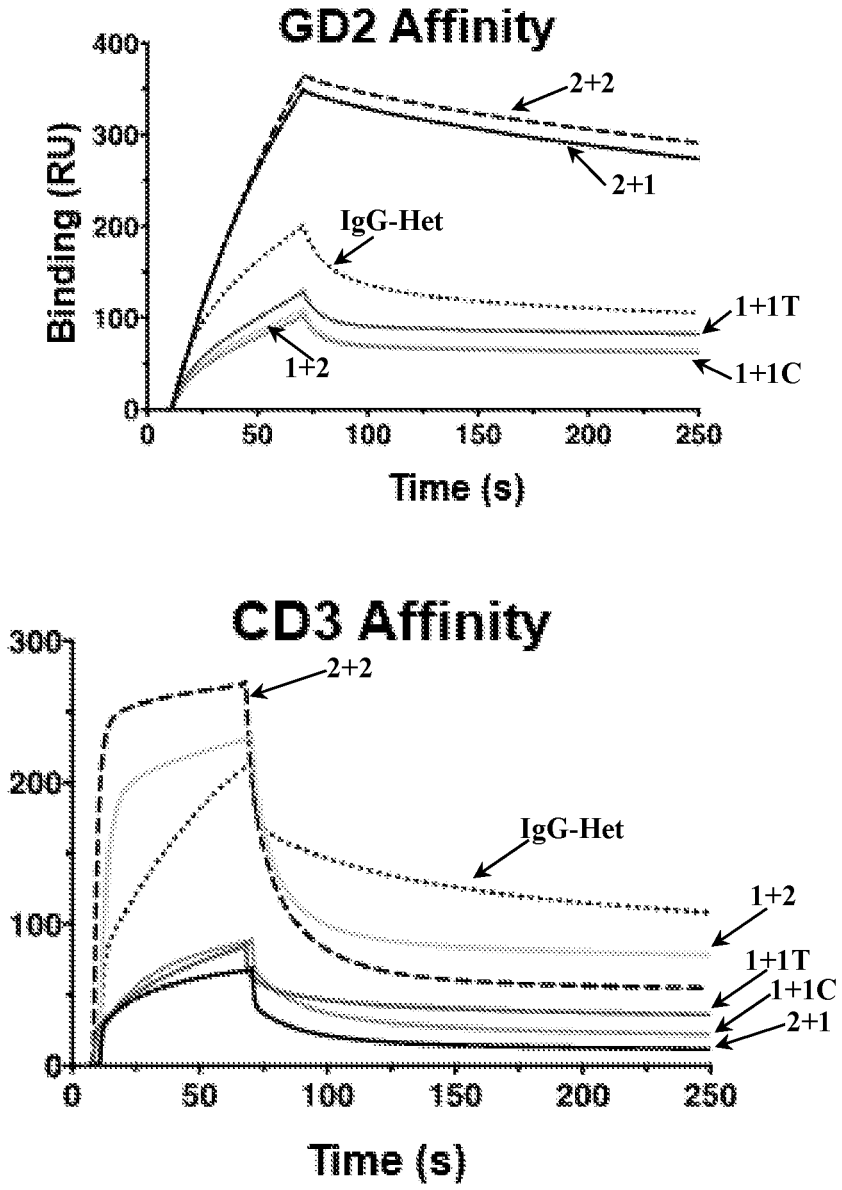

GD2 Affinity
Binding (RU)
Time (s)
2+2
2+1
IgG-Het
1+1T
1+2
1+1C
CD3 Affinity
Time (s)
2+2
IgG-Het
1+2
1+1T
1+1C
2+1

Figure 4 (cont.)

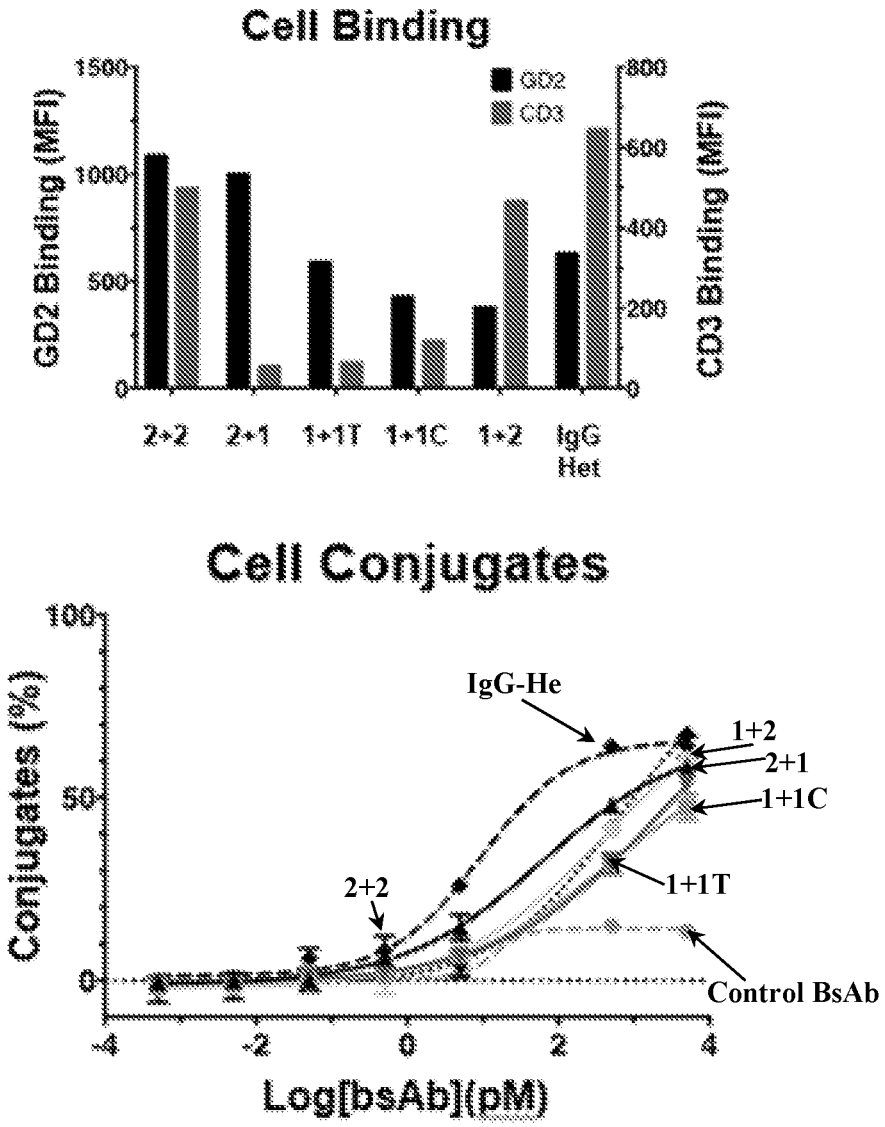


Figure 5

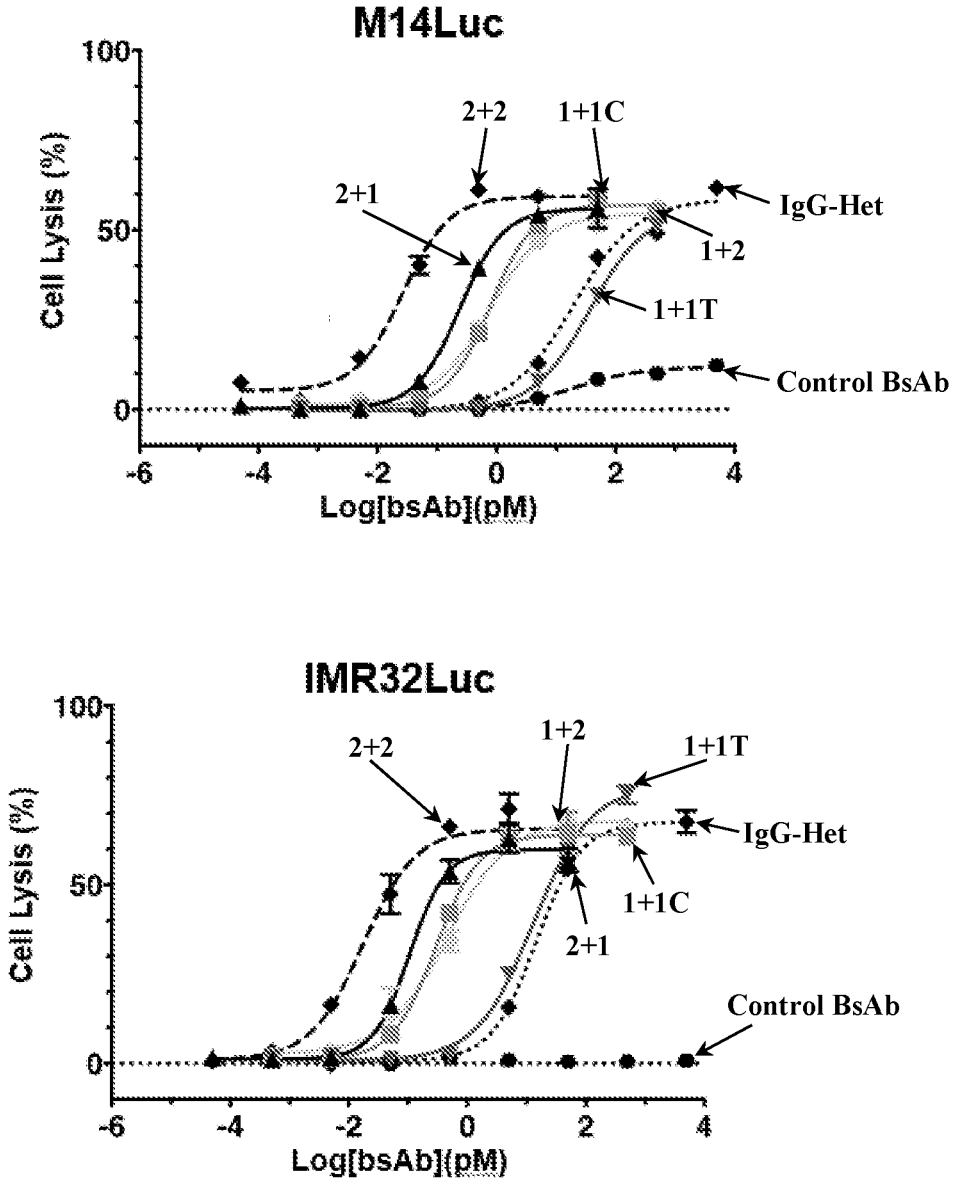
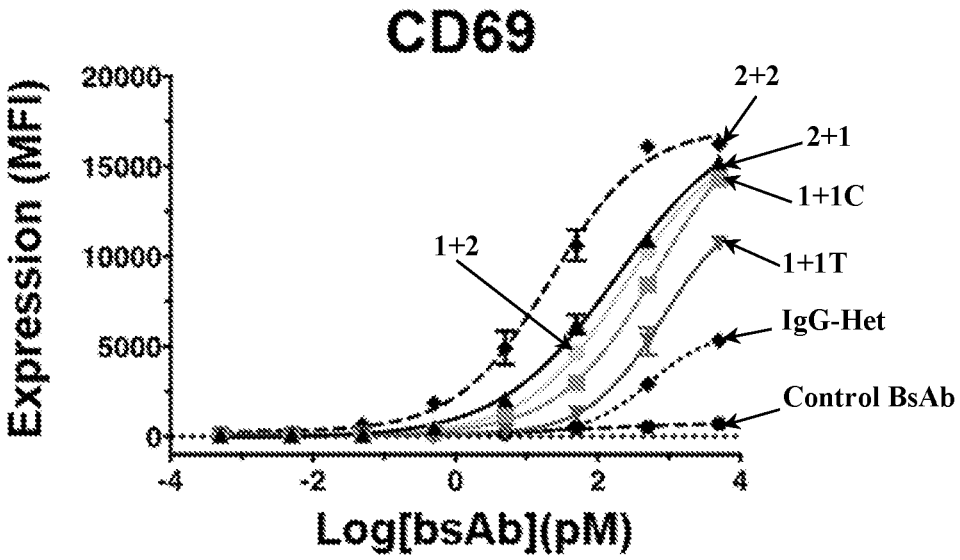

M14Luc
Cell Lysis (%)
100
50
0
-6
-4
-2
0
2
4
Log[bsAb](pM)
2+2
1+1C
2+1
IgG-Het
1+2
1+1T
Control BsAb
IMR32Luc
Cell Lysis (%)
100
50
0
-6
-4
-2
0
2
4
Log[bsAb](pM)
2+2
1+2
1+1T
IgG-Het
1+1C
2+1
Control BsAb

Figure 6


CD69
Expression (MFI)
20000
15000
10000
5000
0
-4
-2
0
2
4
Log[bsAb](pM)
2+2
2+1
1+1C
1+2
1+1T
IgG-Het
Control BsAb

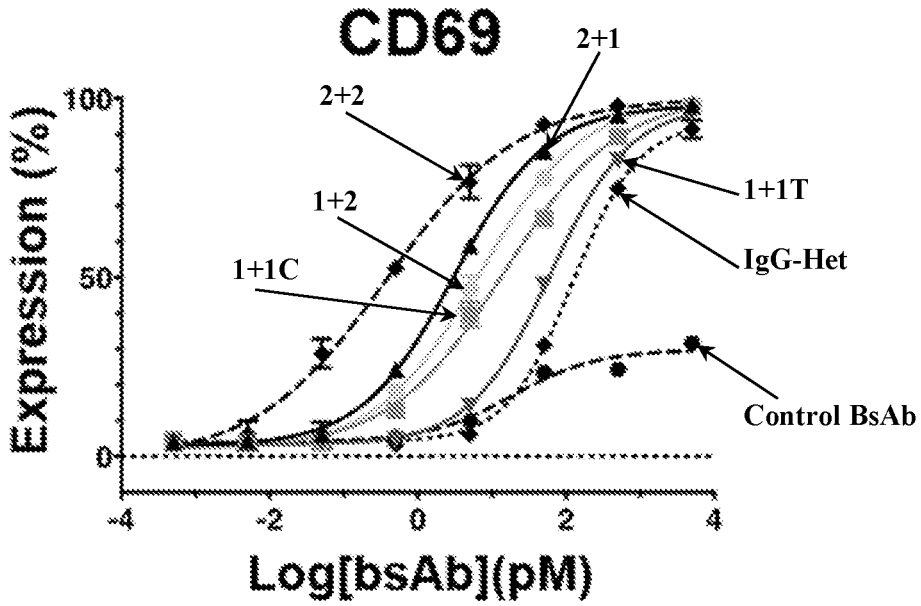
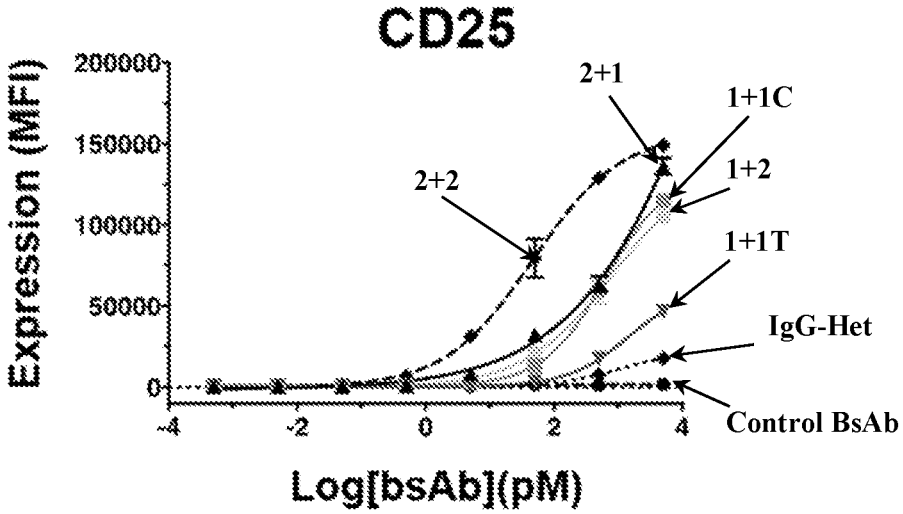

CD69
Expression (%)
100
50
0
-4
-2
0
2
4
Log[bsAb](pM)
2+1
2+2
1+2
1+1C
1+1T
IgG-Het
Control BsAb

Figure 6 (cont.)



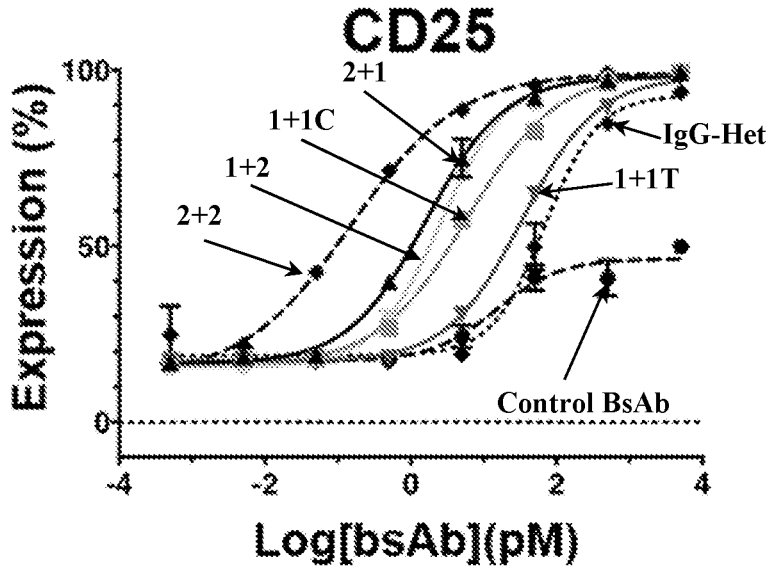


Figure 6 (cont.)

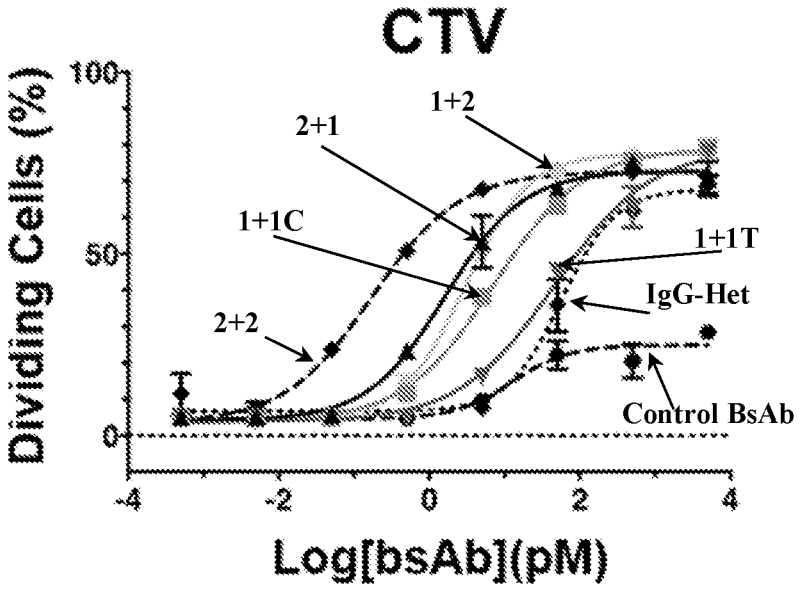


Figure 7

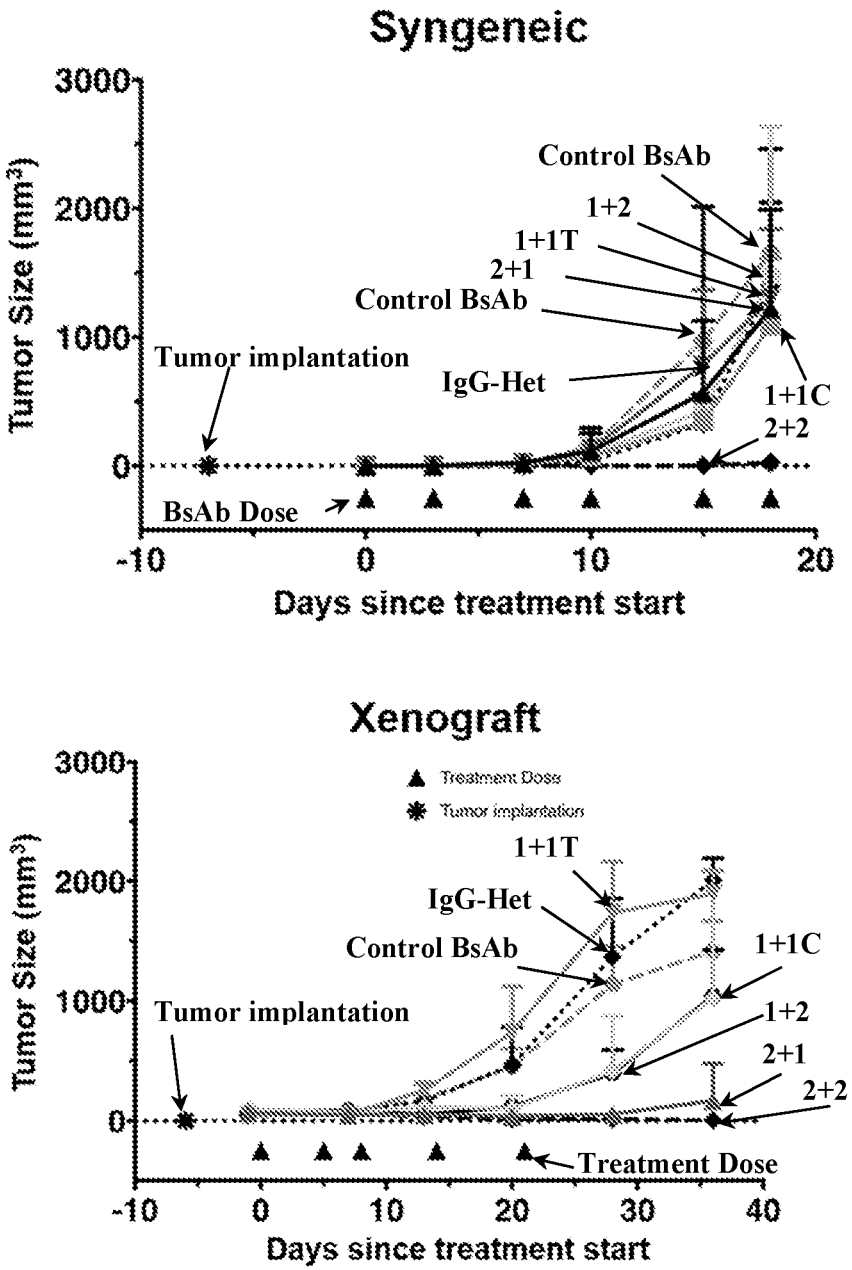

Syngeneic
Tumor Size (mm³)
3000
2000
1000
0
Control BsAb
1+2
1+1T
2+1
Control BsAb
Tumor implantation
IgG-Het
1+1C
2+2
BsAb Dose
-10
0
10
20
Days since treatment start
Xenograft
Tumor Size (mm³)
3000
2000
1000
0
Treatment Dose
Tumor implantation
1+1T
IgG-Het
Control BsAb
1+1C
Tumor implantation
1+2
2+1
2+2
Treatment Dose
-10
0
10
20
30
40
Days since treatment start

Figure 8

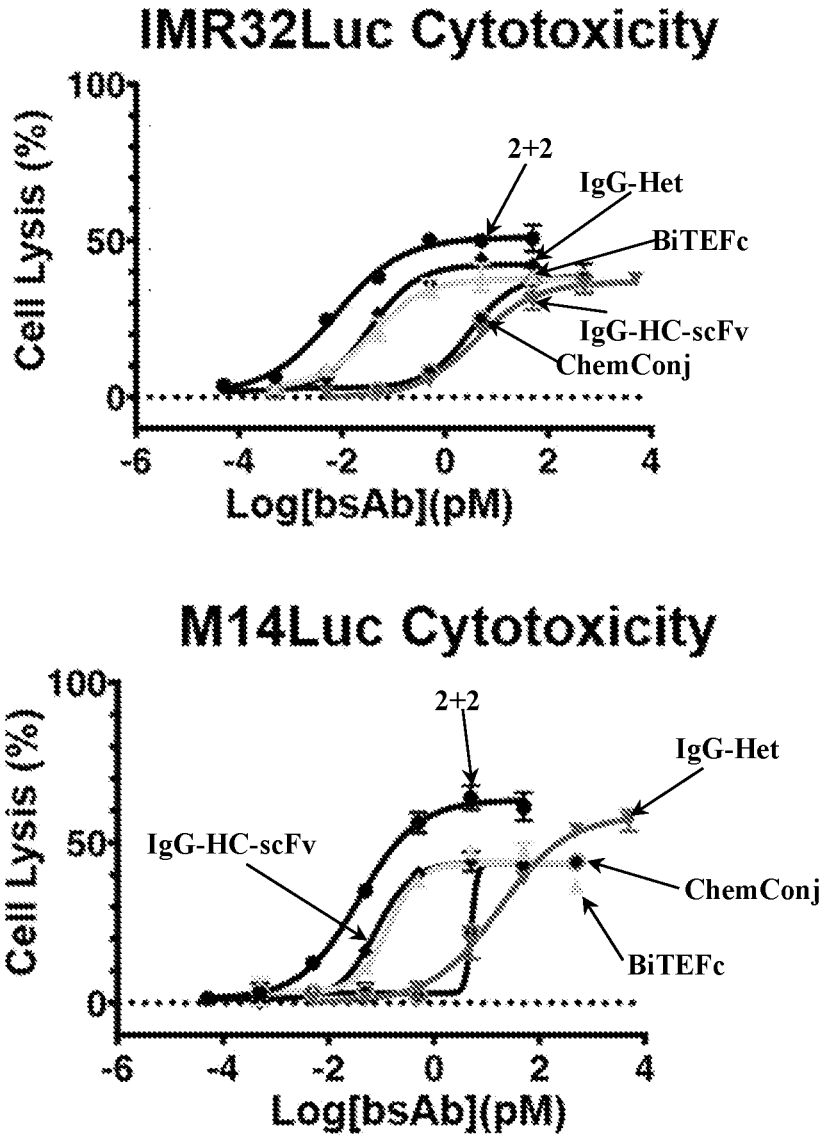
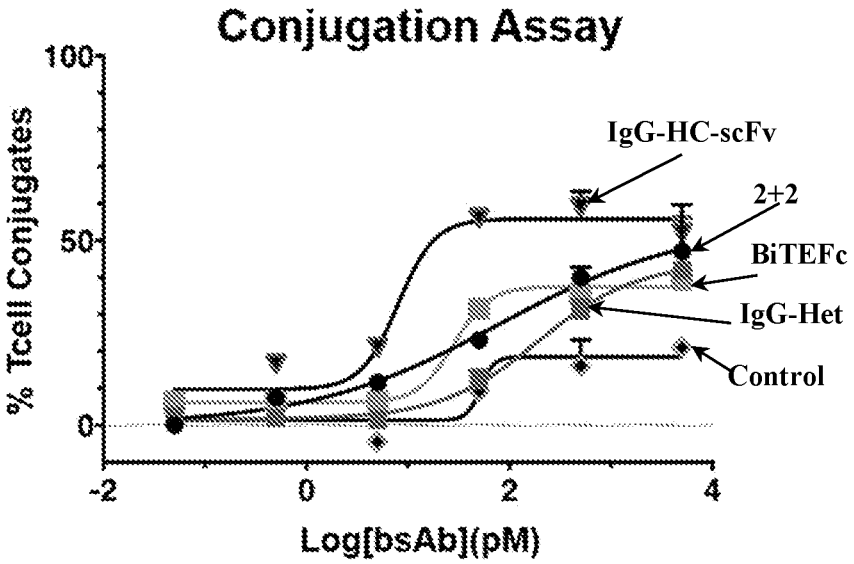

IMR32Luc Cytotoxicity
Cell Lysis (%)
100
50
0
-6
-4
-2
0
2
4
Log[bsAb](pM)
2+2
IgG-Het
BiTEFc
IgG-HC-scFv
ChemConj
M14Luc Cytotoxicity
Cell Lysis (%)
100
50
0
-6
-4
-2
0
2
4
Log[bsAb](pM)
2+2
IgG-Het
IgG-HC-scFv
ChemConj
BiTEFc

Figure 8 (cont.)



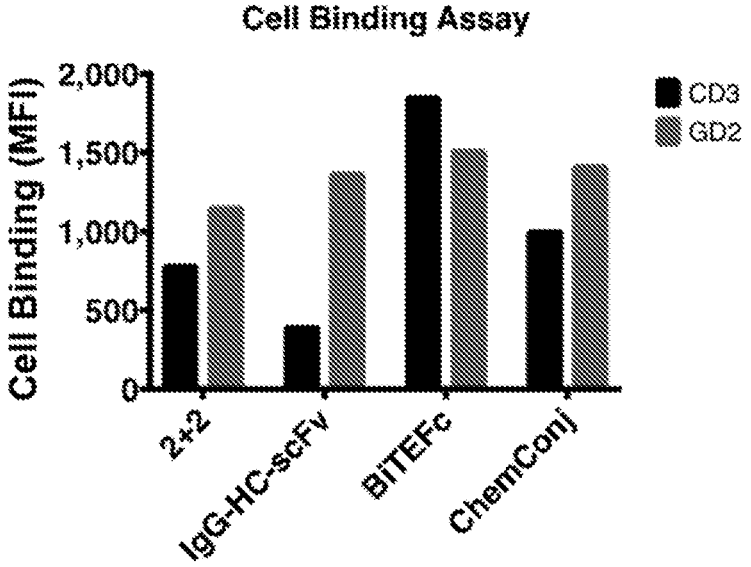


Figure 9

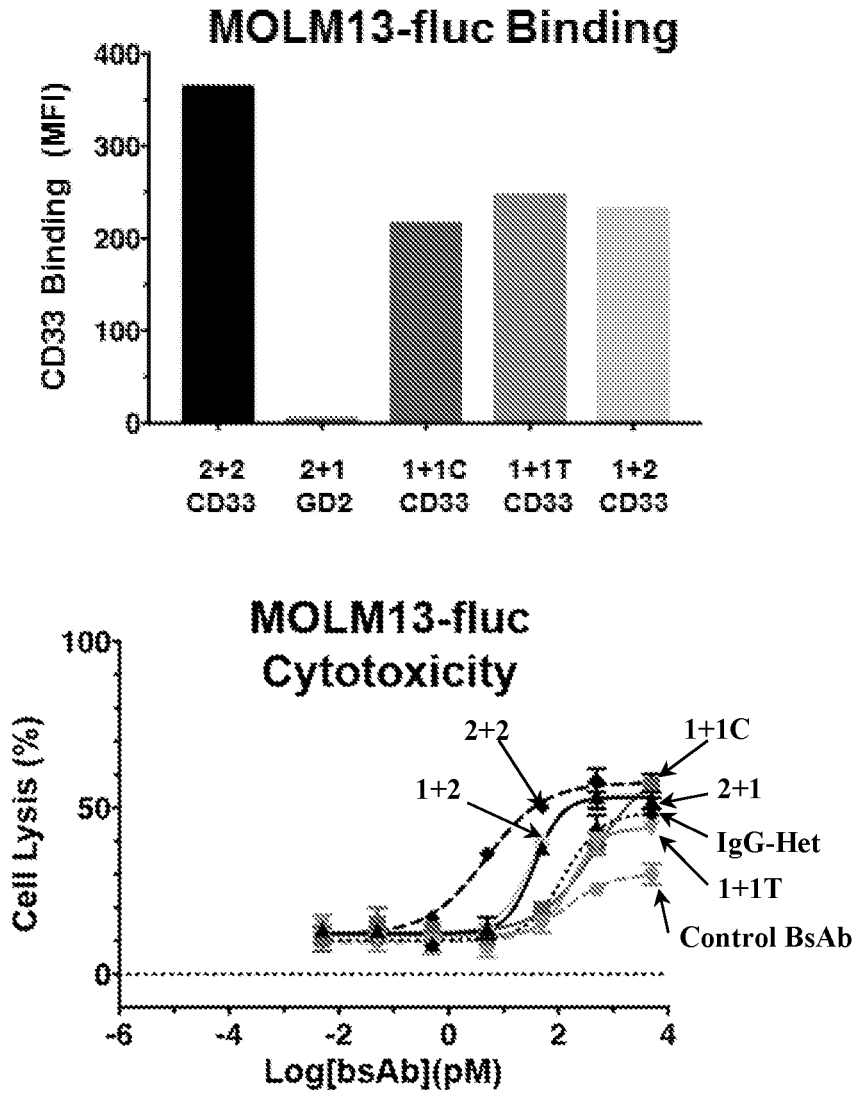

MOLM13-fluc Binding
CD33 Binding (MFI)
400
300
200
100
0
2+2 CD33
2+1 GD2
1+1C CD33
1+1T CD33
1+2 CD33
MOLM13-fluc Cytotoxicity
Cell Lysis (%)
100
50
0
-6
-4
-2
0
2
4
Log[bsAb](pM)
2+2
1+2
1+1C
2+1
IgG-Het
1+1T
Control BsAb

Figure 9 (cont.)

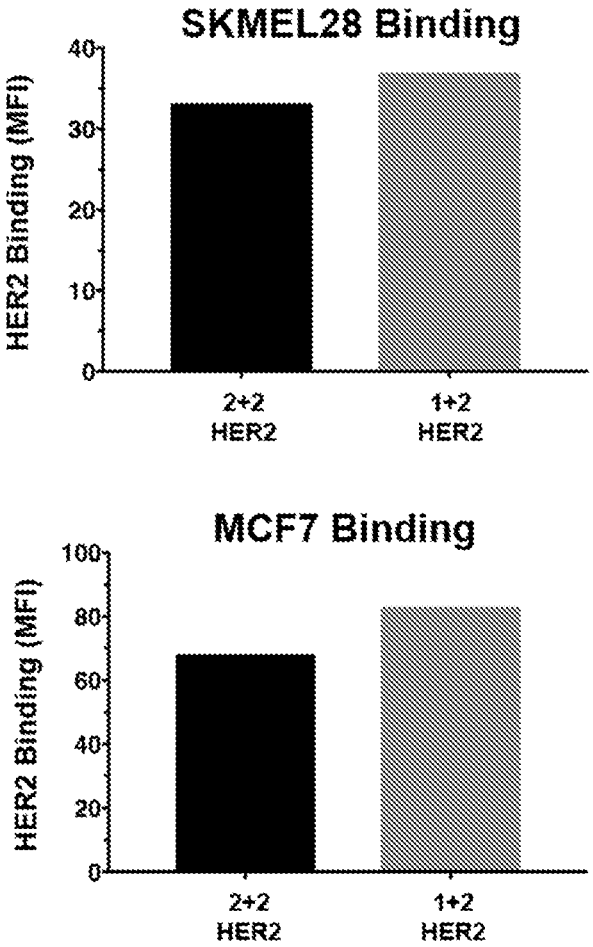


Figure 10a

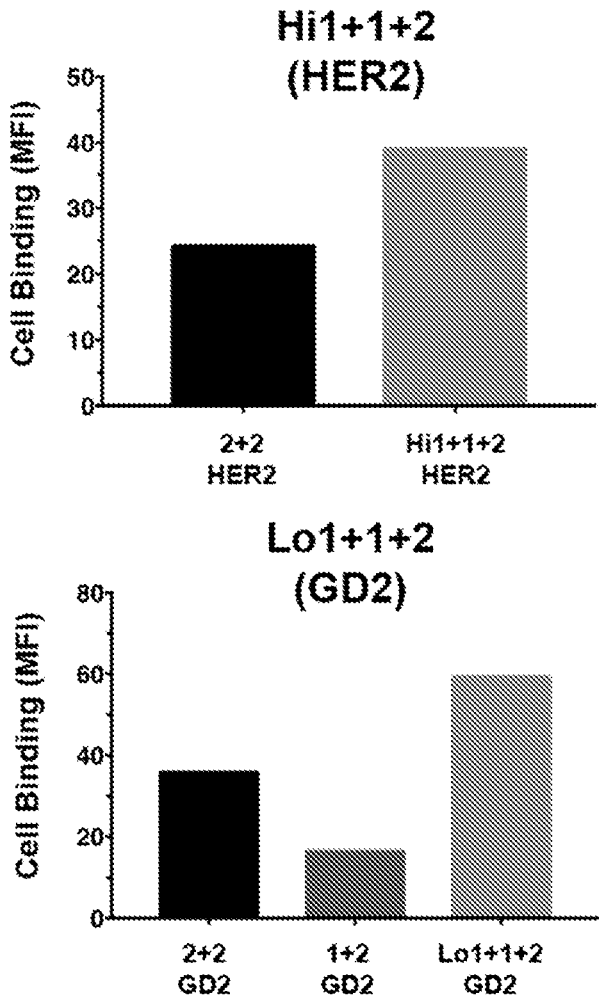

Hi1+1+2
(HER2)
Cell Binding (MFI)
50
40
30
20
10
0
2+2
HER2
Hi1+1+2
HER2
Lo1+1+2
(GD2)
Cell Binding (MFI)
80
60
40
20
0
2+2
GD2
1+2
GD2
Lo1+1+2
GD2

Figure 10a (cont.)

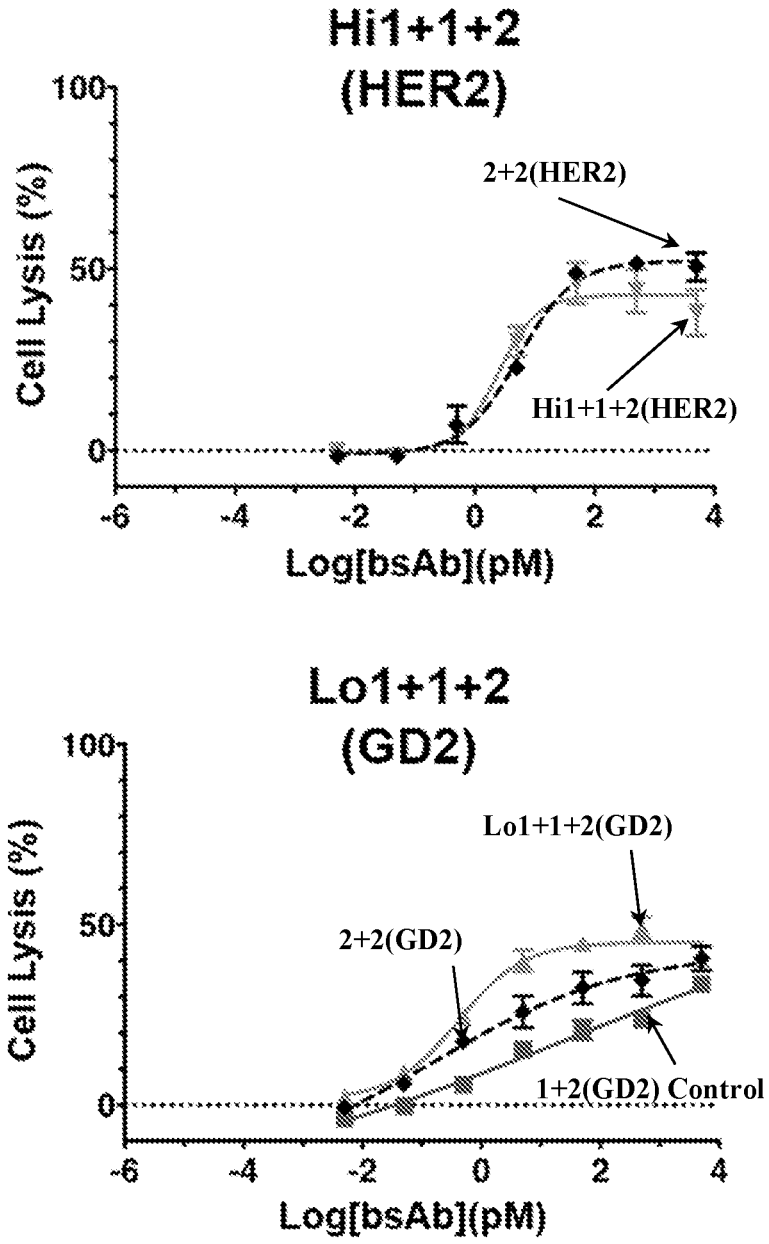


Figure 10b

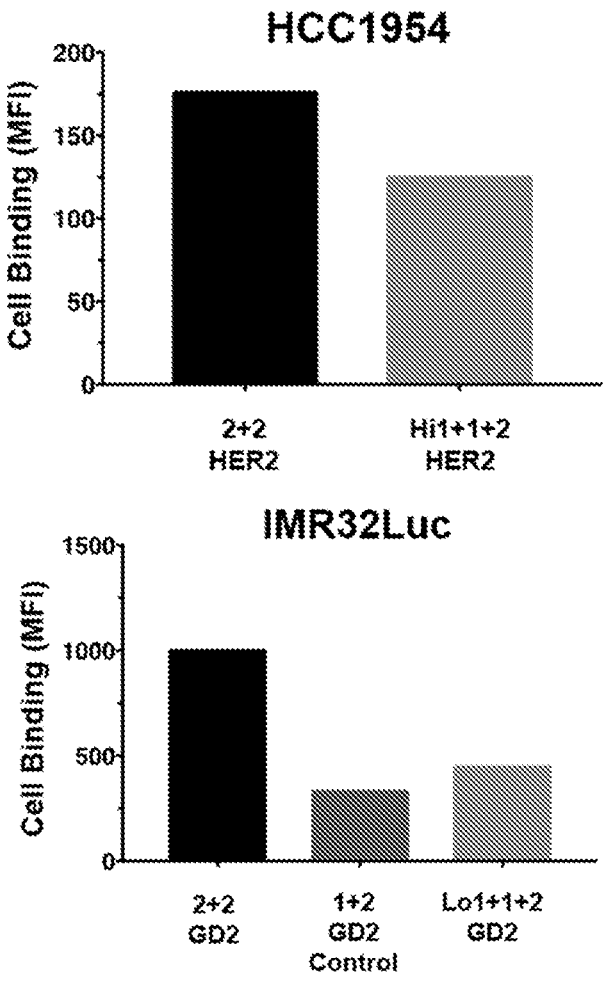

HCC1954
Cell Binding (MFI)
200
150
100
50
0
2+2
HER2
Hi1+1+2
HER2
IMR32Luc
Cell Binding (MFI)
1500
1000
500
0
2+2
GD2
1+2
GD2
Control
Lo1+1+2
GD2

Figure 10b (cont.)

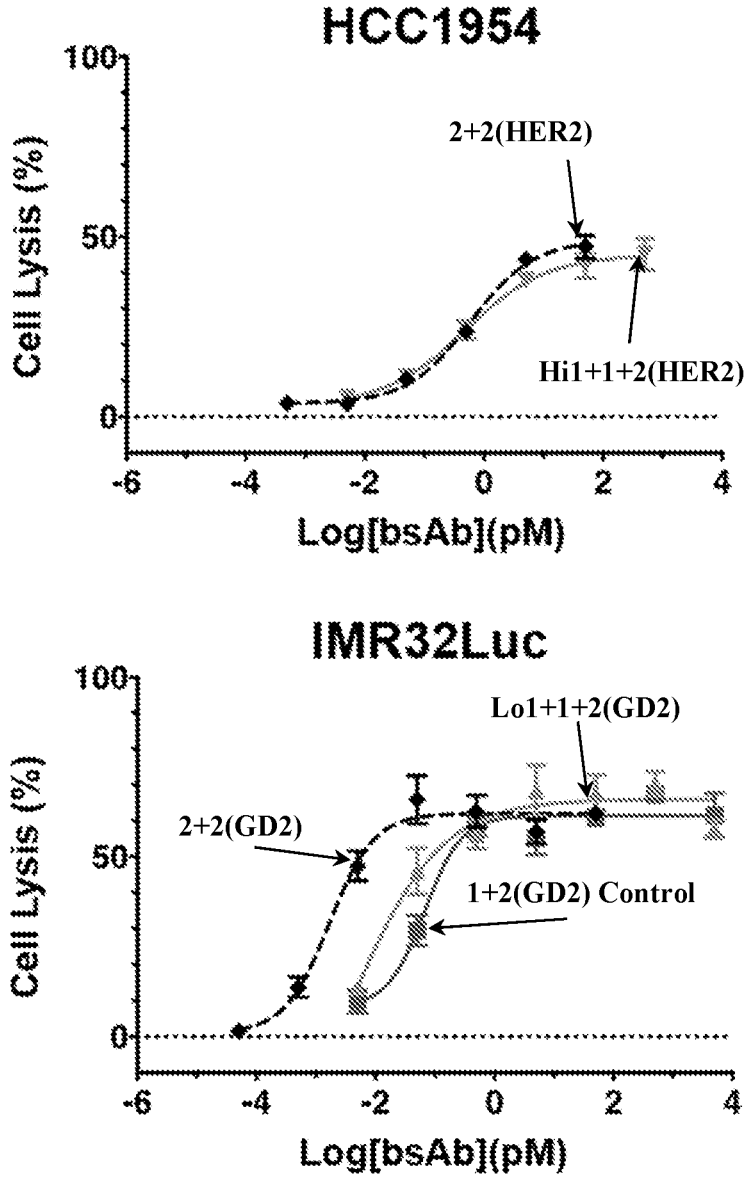


Figure 11a

First CH2-CH3 domain	Second CH2-CH3 domain
F405A	T394F
S364D	Y349K
S364E	L368K
S364E	Y349K
S364F	K370G
S364H	Y349K
S364H	Y349T
S364Y	K370G
T411K	K370E
V397S/F405A	T394F
K370R/T411K	K370E/T411E
L351E/S364D	Y349K/L351K
L351E/S364E	Y349K/L351K
L351E/T366D	L351K/T366K
P395T/V397S/F405A	T394F
S364D/K370G	S364Y/K370R
S364D/T394F	Y349K/F405A
S364E/F405A	Y349K/T394F
S364E/F405S	Y349K/T394Y
S364E/T411E	Y349K/D401K
S364H/D401K	Y349T/T411E
S364H/F405A	Y349T/T394F
S364H/T394F	Y349T/F405A
Y349C/S364E	Y349K/S354C
L351E/S364D/F405A	Y349K/L351K/T394F
L351K/S364H/D401K	Y349T/L351E/T411E
S364E/T411E/F405A	Y349K/T394F/D401K
S364H/D401K/F405A	Y349T/T394F/T411E
S364H/F405A/T411E	Y349T/T394F/D401K
Y349T	S364H
T394F	F405A
Y349T/T394F	S364H/F405A
K370E	T411K
K370E/T411D	T411R
K370E/T411E	K370R/T411K
L368E/K409E	L368K
Y349T/T411E	S364H/D401K
Y349T/T394F/S354C	S364H/F405A/Y349C
T411E	D401K
T411E	D401R/T411R
Q347E/K360E	Q347R
L368E	S364K
L368E/K370G	S364K
L368E/K370T	S364K
L368E/D401R	S364K
L368E/D401N	S364K
L368E	E357Q/S364K
L368E	S364K/K409E
L368E	S364K/E357V
L368D	S364K

Figure 11b

First CH2-CH3 domain	Second CH2-CH3 domain
F405A	T394F
S364D	Y349K
S364E	Y349K
S364H	Y349T
L351K	L351E
D401K	T411E
S364D/T394F	Y349K/F405A
S364E/F405A	Y349K/T394F
S364H/D401K	Y349T/T411E
S364H/F405A	Y349T/T394F
S364H/T394F	Y349T/F405A
L351K/S364H/D401K	Y349T/L351E/T411E
S364H/D401K/F405A	Y349T/T394F/T411E
S364H/F405A/T411E	Y349T/T394F/D401K
Y349T	S364H
T394F	F405A
Y349T/T394F	S364H/F405A
K370E	T411K
K370E/T411D	T411K
K370E/T411E	K370R/T411K
L368E/K409E	L368K
Y349T/T411E	S364H/D401K
Y349T/T394F/S354C	S364H/F405A/Y349C
T411E	D401K
T411E	D401R/T411R
Q347E/K360E	Q347R
L368E	S364K
L368E/K370S	S364K
L368E/K370T	S364K
L368E/D401R	S364K
L368E/D401N	S364K
L368E	E357S/S364K
L368E	S364K/K409E
L368E	S364K/K409V
L368D	S364K

Figure 11c

First CH2-CH3 domain	Second CH2-CH3 domain
Y407T	T366Y
F405A	T394W
T366Y/F405A	T394W/Y407T
Y407A	T366W
T366S/L368A/Y407V	T366W
T366S/L368A/Y407V/Y349C	T366W/S354C
K392D/K409D	E356K/D399K
K370D/K392D/K409D	E356K/E357K/D399K
Y349T	S364H
T394F	F405A
Y349T/T394F	S364H/F405A
K370E	T411K
K370E/T411D	T411K
K370E/T411E	K370R/T411K
L368E/K409E	L368K
Y349T/T411E	S364H/D401K
Y349T/T394F/S354C	S364H/F405A/Y349C
T411E	D401K
T411E	D401R/T411R
Q347E/K360E	Q347R
L368E	S364K
I199T/N203D/K247Q/R355Q/N384S/K392N/V397M/Q419E/K447_ (deletion of K447)	Q196K/I199T/P217R/P228R/N276K
I199T/N203D/K247Q/R355Q/N384S/K392N/V397M/Q419E/K447_	Q196K/I199T/N276K
N384S/K392N/V397M/Q419E	N276K
D221E/P228E/L368E	D221R/P228R/K409R
C220E/P228E/L368E	C220R/E224R/P228R/K409R
F405L	K409R
T366I/K392M/T394W	F405A/Y407V
T366V/K409F	L351Y/Y407A
T366A/K392E/K409F/T411E	D399R/S400R/Y407A
Y349T	S364H
T394F	F405A
Y349T/T394F	S364H/F405A
K370E	T411K
K370E/T411D	T411K
K370E/T411E	K370R/T411K
L368E/K409E	L368K
Y349T/T411E	S364H/D401K
Y349T/T394F/S354C	S364H/F405A/Y349C
T411E	D401K
T411E	D401R/T411R

Figure 11d

First CH2-CH3 domain	Second CH2-CH3 domain
Q347E/K360E	Q347R
L368E	S364K
L368E/K370S	S364K
L368E/K370T	S364K
L368E/D401R	S364K
L368E/D401N	S364K
L368E	E357S/S364K
L368E	S364K/K409E
L368E	S364K/K409V
L368D	S364K

Figure 11e

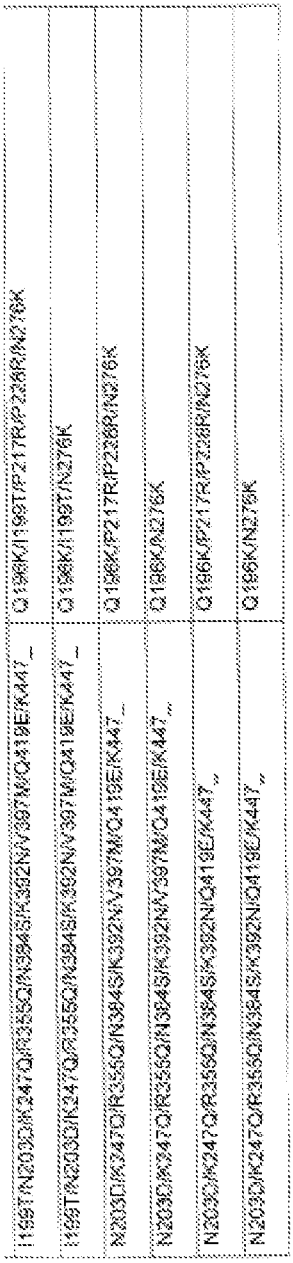

First CH2-CH3 domain
Second CH2-CH3 domain
I199T/N203D/K247Q/R355Q/N384S/K392N/V397M/Q419E/K447_
I199T/N203D/K247Q/R355Q/N384S/K392N/V397M/Q419E/K447_
N203D/K247Q/R355Q/N384S/K392N/V397M/Q419E/K447_
N203D/K247Q/R355Q/N384S/K392N/V397M/Q419E/K447_
N203D/K247Q/R355Q/N384S/K392N/Q419E/K447_
N203D/K247Q/R355Q/N384S/K392N/Q419E/K447_
Q196K/I199T/P217R/P228R/N276K
Q196K/I199T/N276K
Q196K/P217R/P228R/N276K
Q196K/N276K
Q196K/P217R/P228R/N276K
Q196K/N276K

Figure 12a

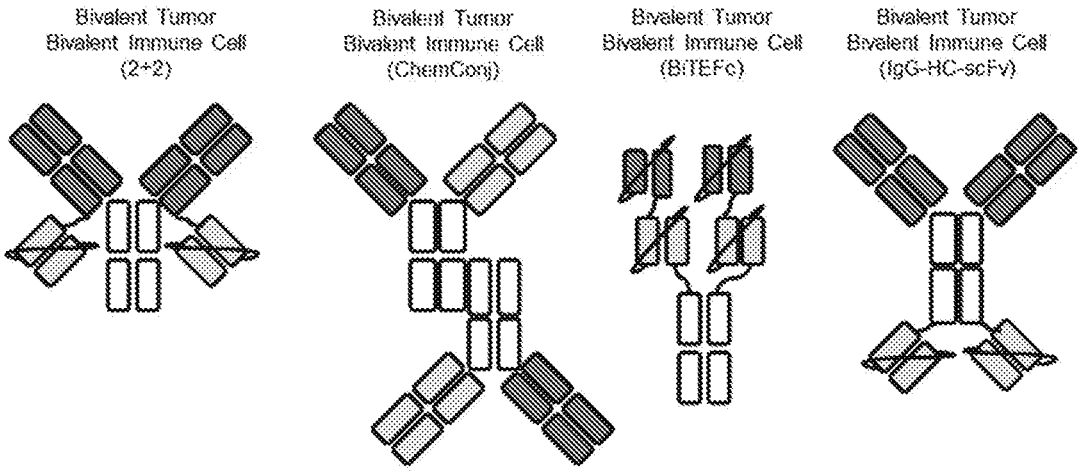


Figure 12b

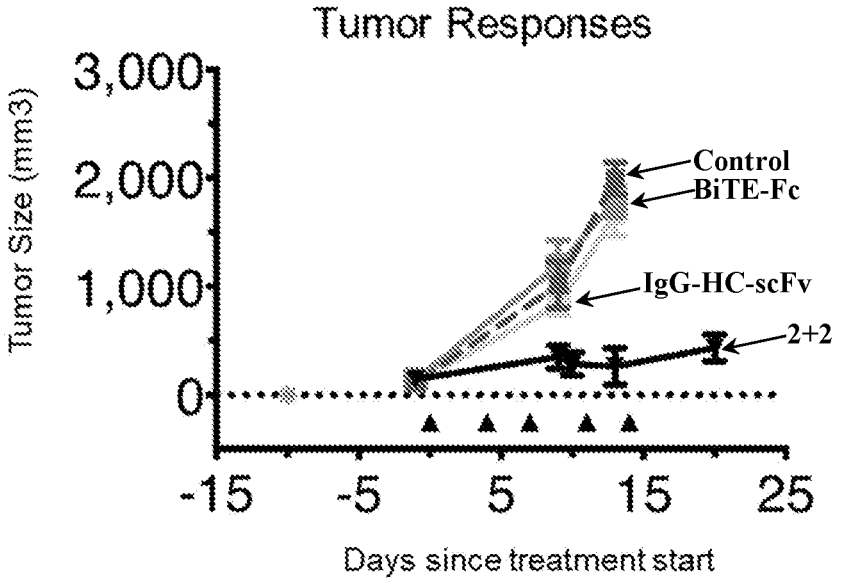


Figure 12c

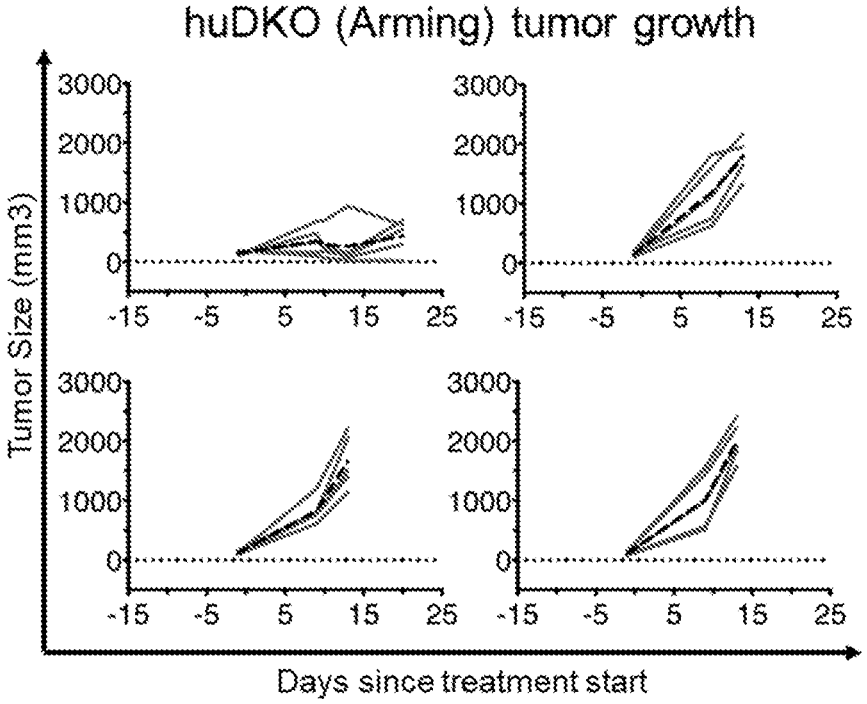
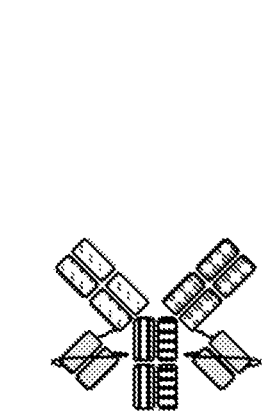

huDKO (Arming) tumor growth
Tumor Size (mm3)
3000
2000
1000
0
-15
-5
5
15
25
Days since treatment start

Figure 13



Monovalent A1
Monovalent A2
Bivalent B
3 Specificities
4 Domains

1+1+2 Lo Affinity
Improved Specificity

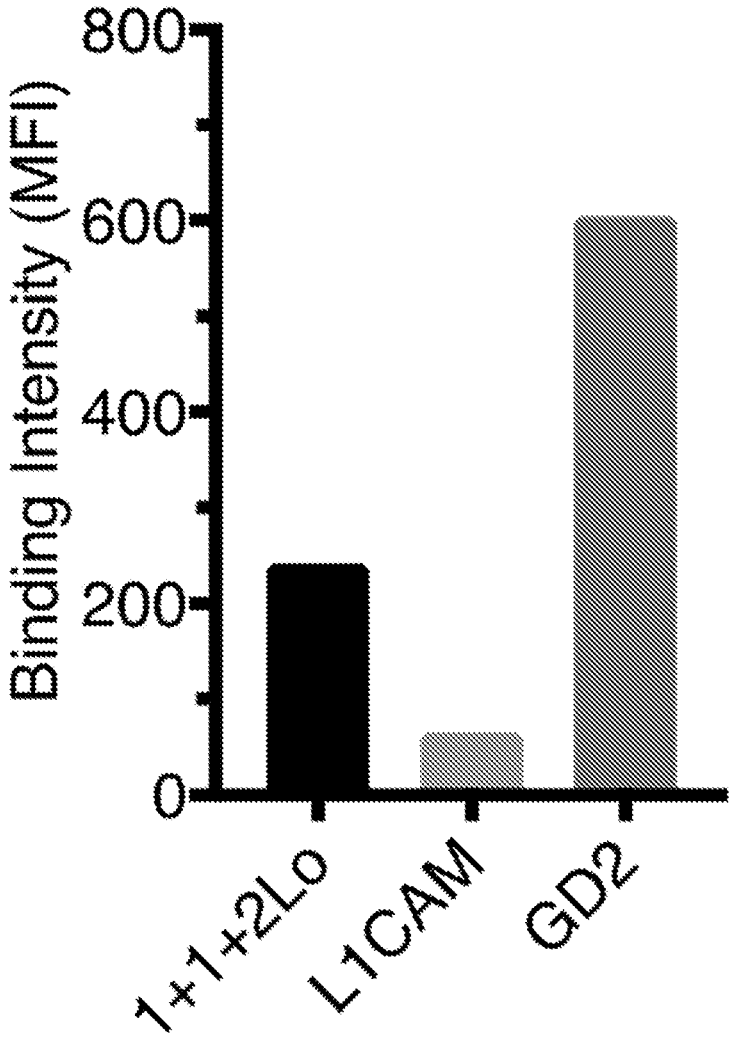


Figure 14

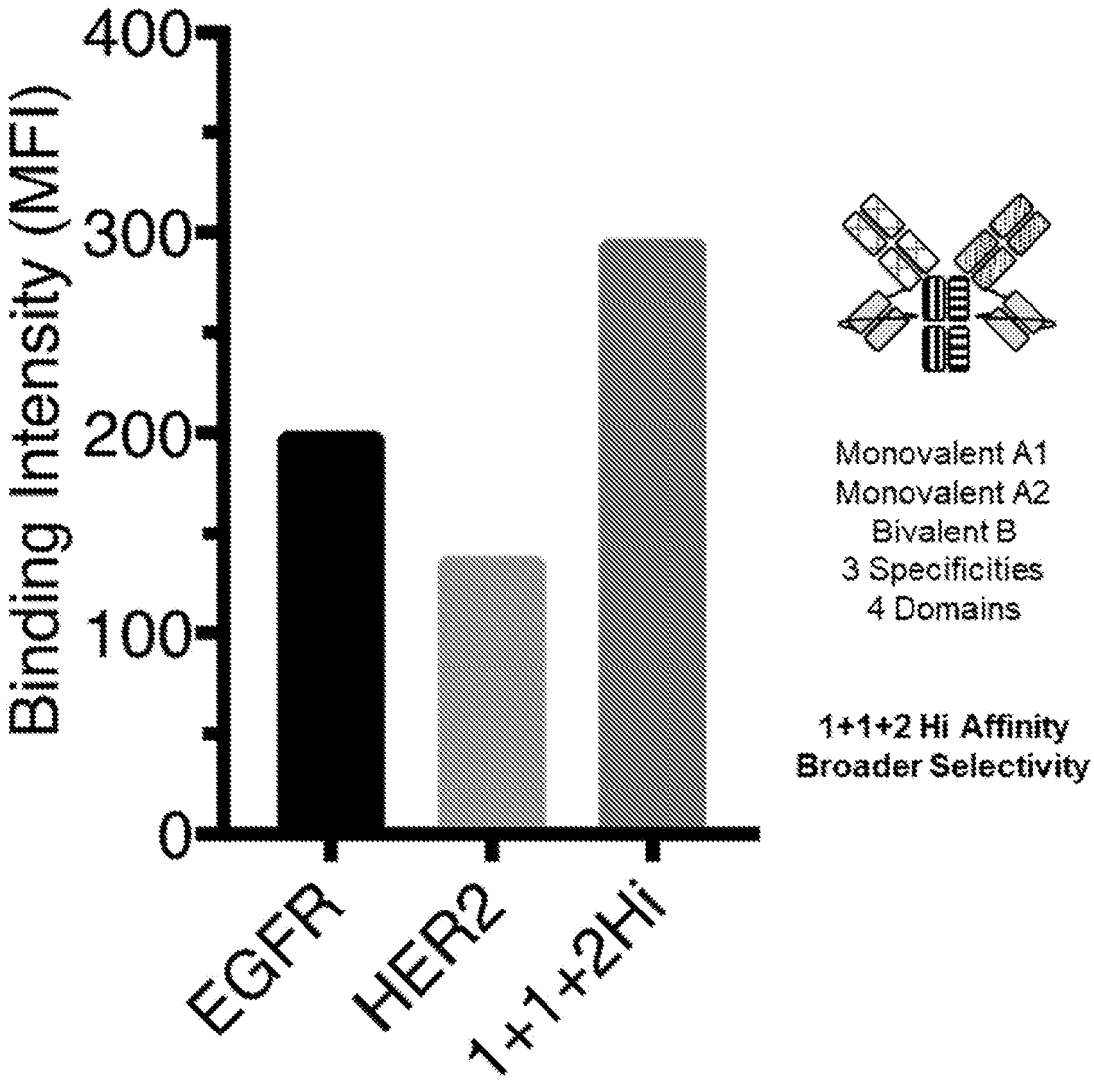

Binding Intensity (MFI)
400
300
200
100
0
EGFR
HER2
1+1+2Hi
Monovalent A1
Monovalent A2
Bivalent B
3 Specificities
4 Domains
1+1+2 Hi Affinity
Broader Selectivity

Figure 15

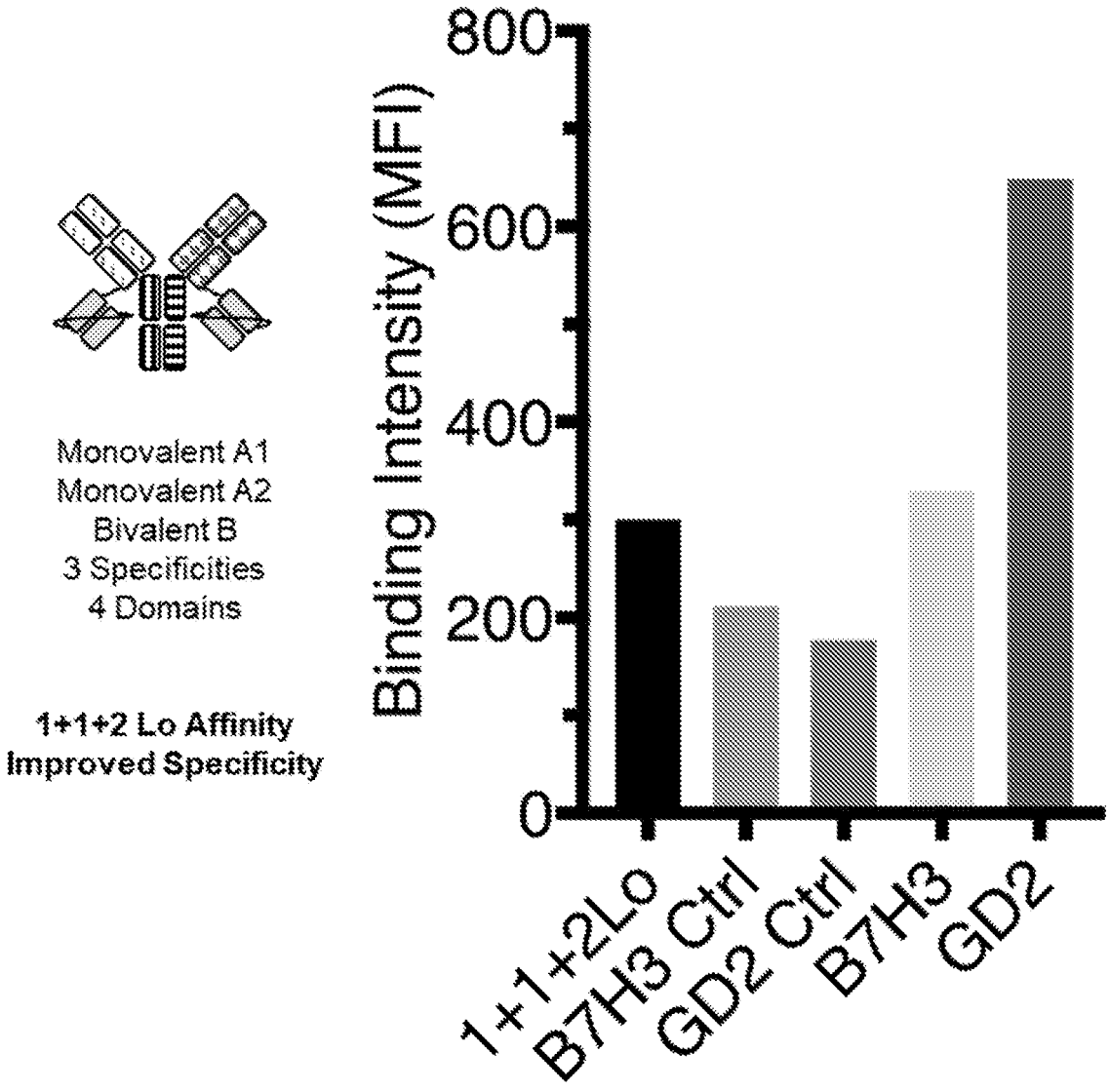
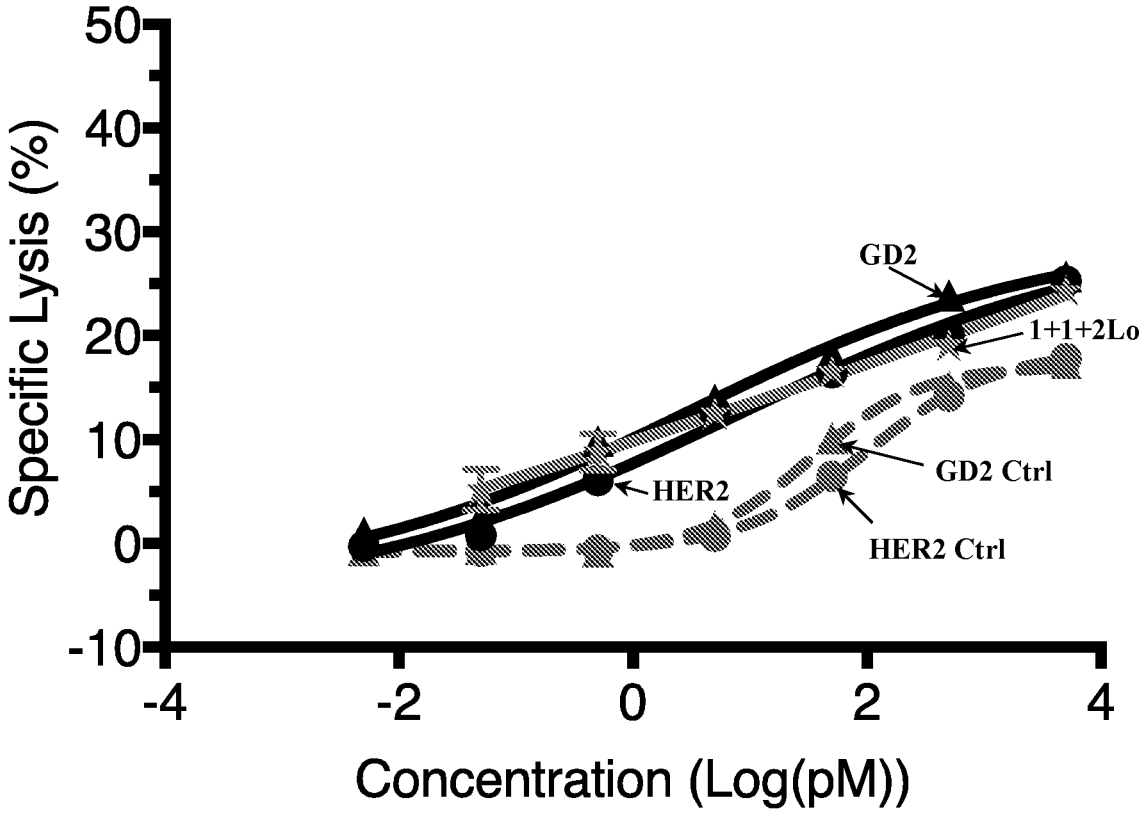
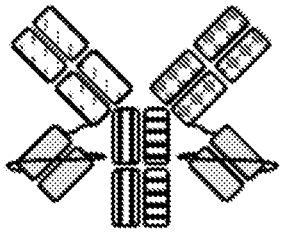

Monovalent A1
Monovalent A2
Bivalent B
3 Specificities
4 Domains
1+1+2 Lo Affinity
Improved Specificity
Binding Intensity (MFI)
800
600
400
200
0
1+1+2Lo
B7H3 Ctrl
GD2 Ctrl
B7H3
GD2

Figure 16

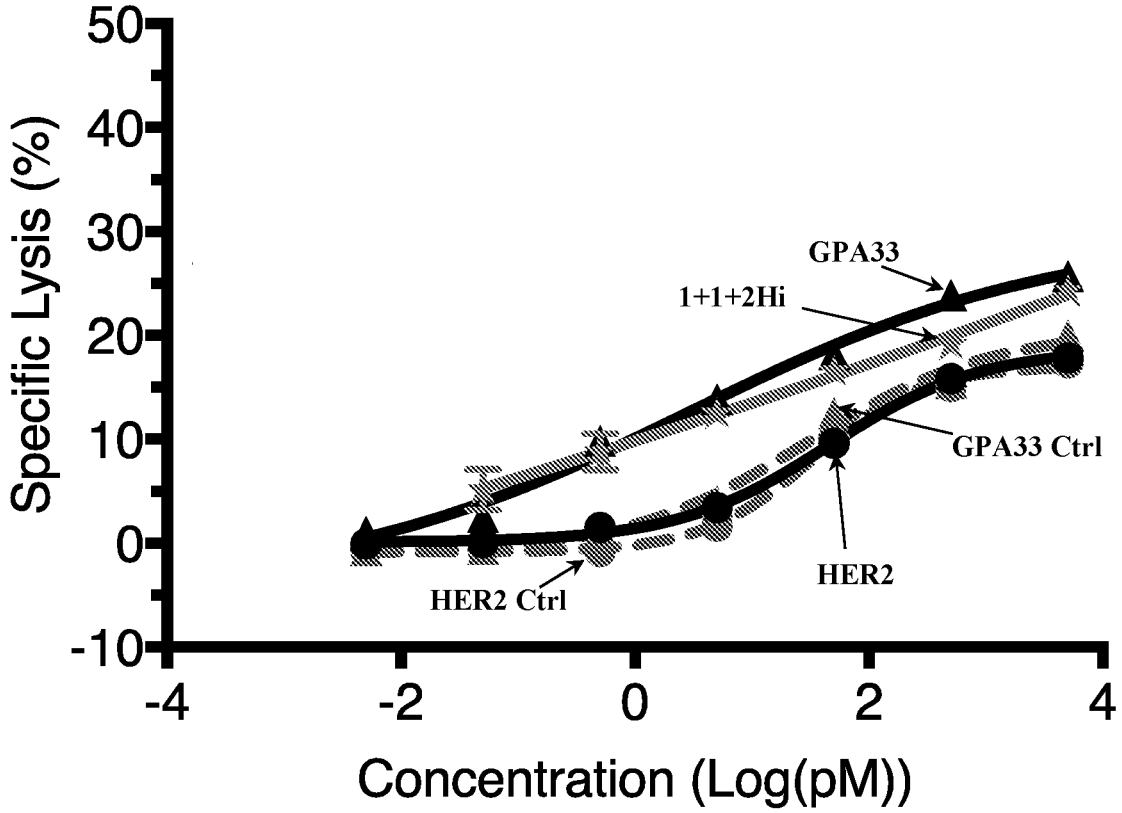


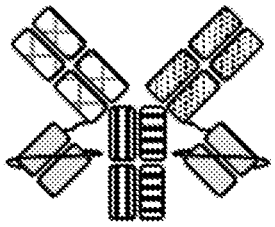


Monovalent A1
Monovalent A2
Bivalent B
3 Specificities
4 Domains

1+1+2 Lo Affinity
Improved Specificity

Figure 17a





Monovalent A1
Monovalent A2
Bivalent B
3 Specificities
4 Domains

1+1+2 Hi Affinity
Broader Selectivity

Figure 17b

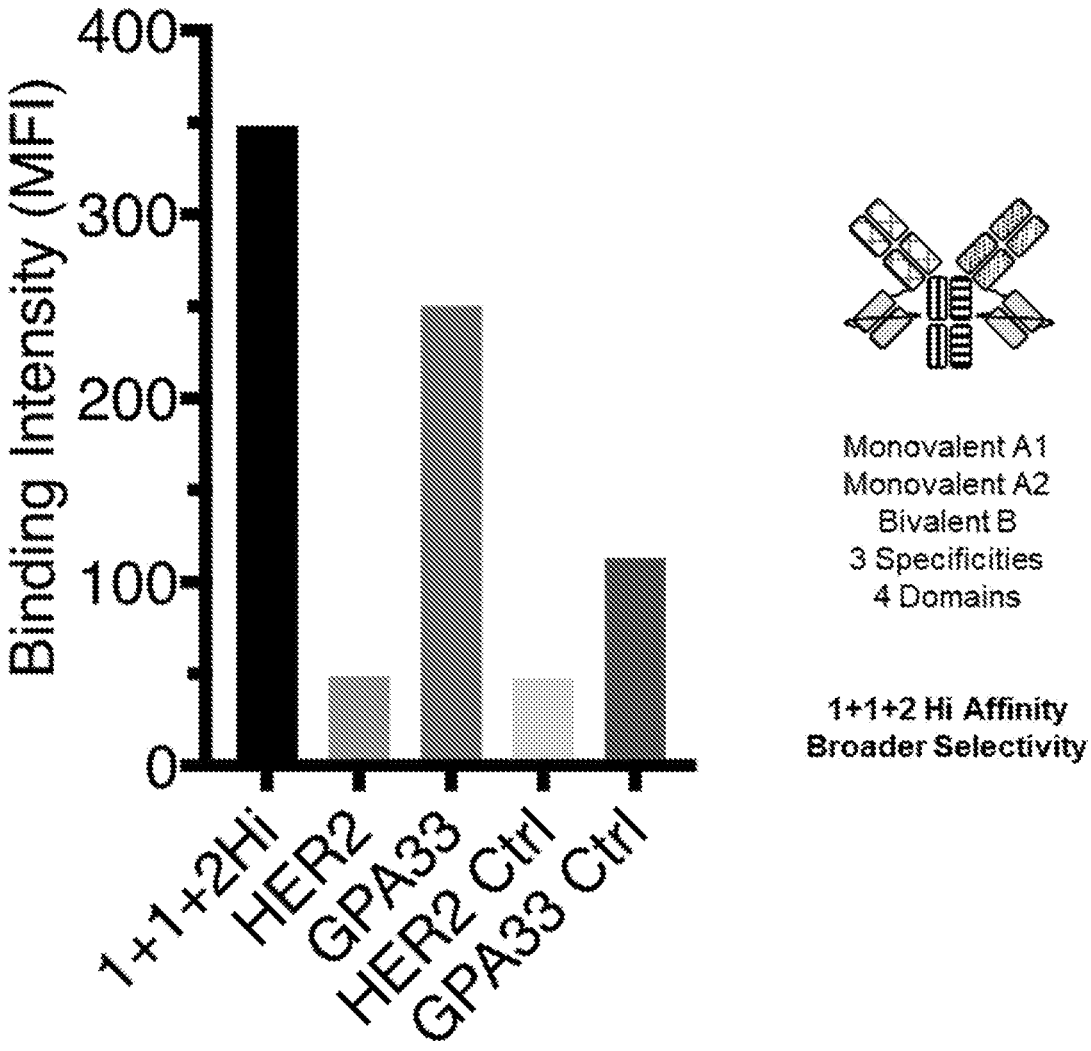
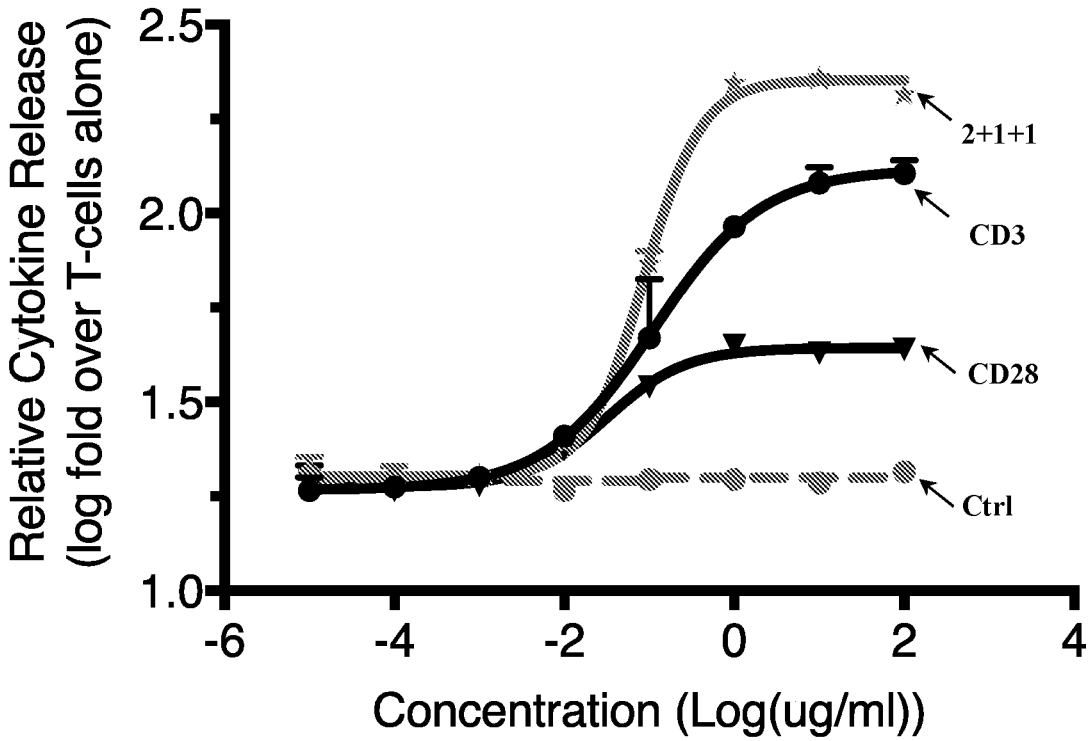
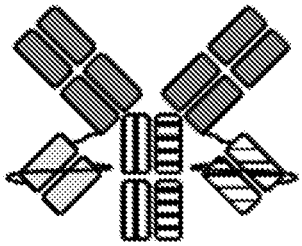

Binding Intensity (MFI)
400
300
200
100
0
1+1+2Hi
HER2
GPA33
HER2 Ctrl
GPA33 Ctrl
Monovalent A1
Monovalent A2
Bivalent B
3 Specificities
4 Domains
1+1+2 Hi Affinity
Broader Selectivity

Figure 18





Bivalent A
Monovalent B1
Monovalent B2
3 Specificities
4 Domains

2+1+1
More Immune
Activation

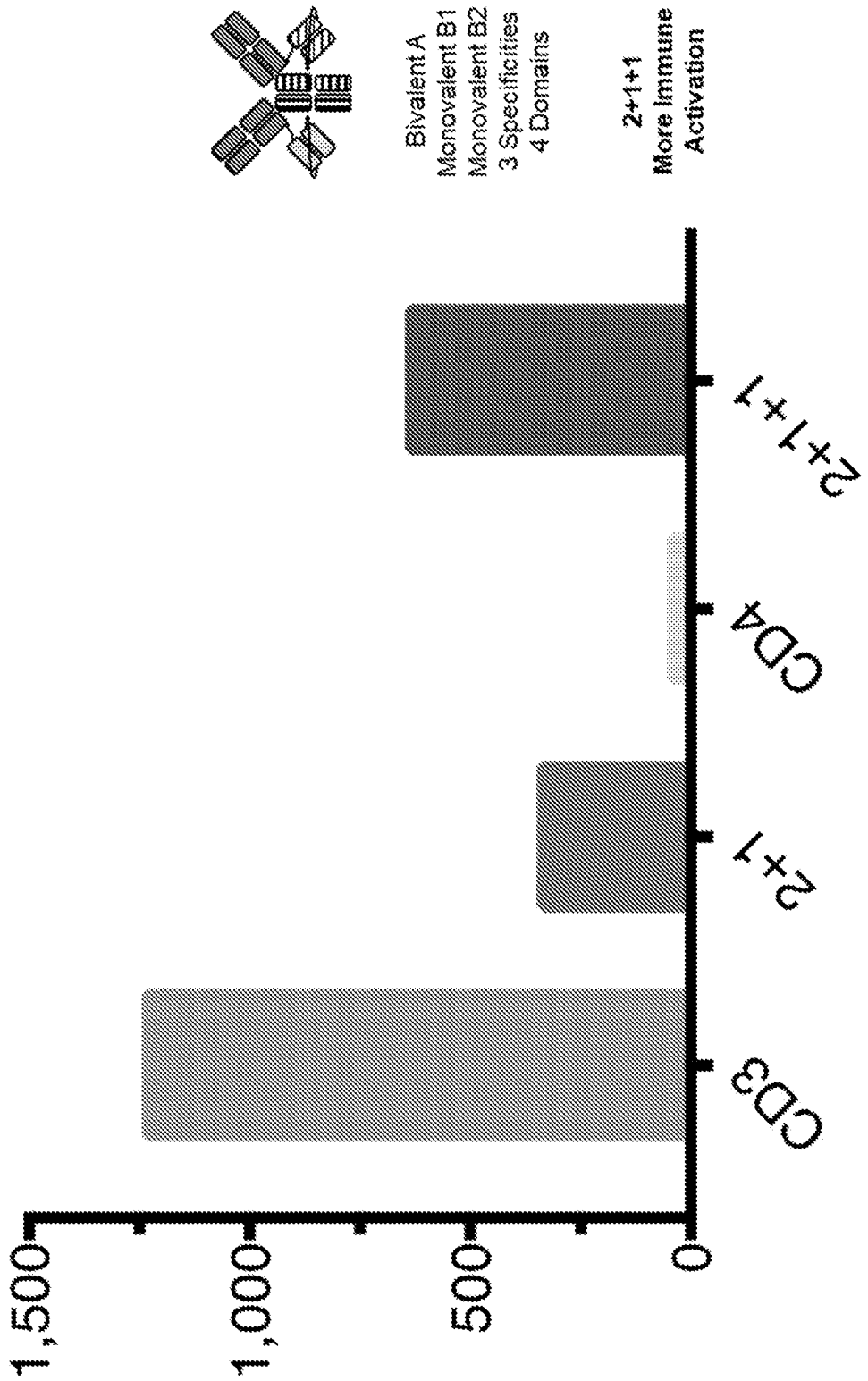

Bivalent A
Monovalent B1
Monovalent B2
3 Specificities
4 Domains
2+1+1
More Immune
Activation
1,500
1,000
500
0
CD3
2+1
CD4
2+1+1

Figure 19

Figure 20

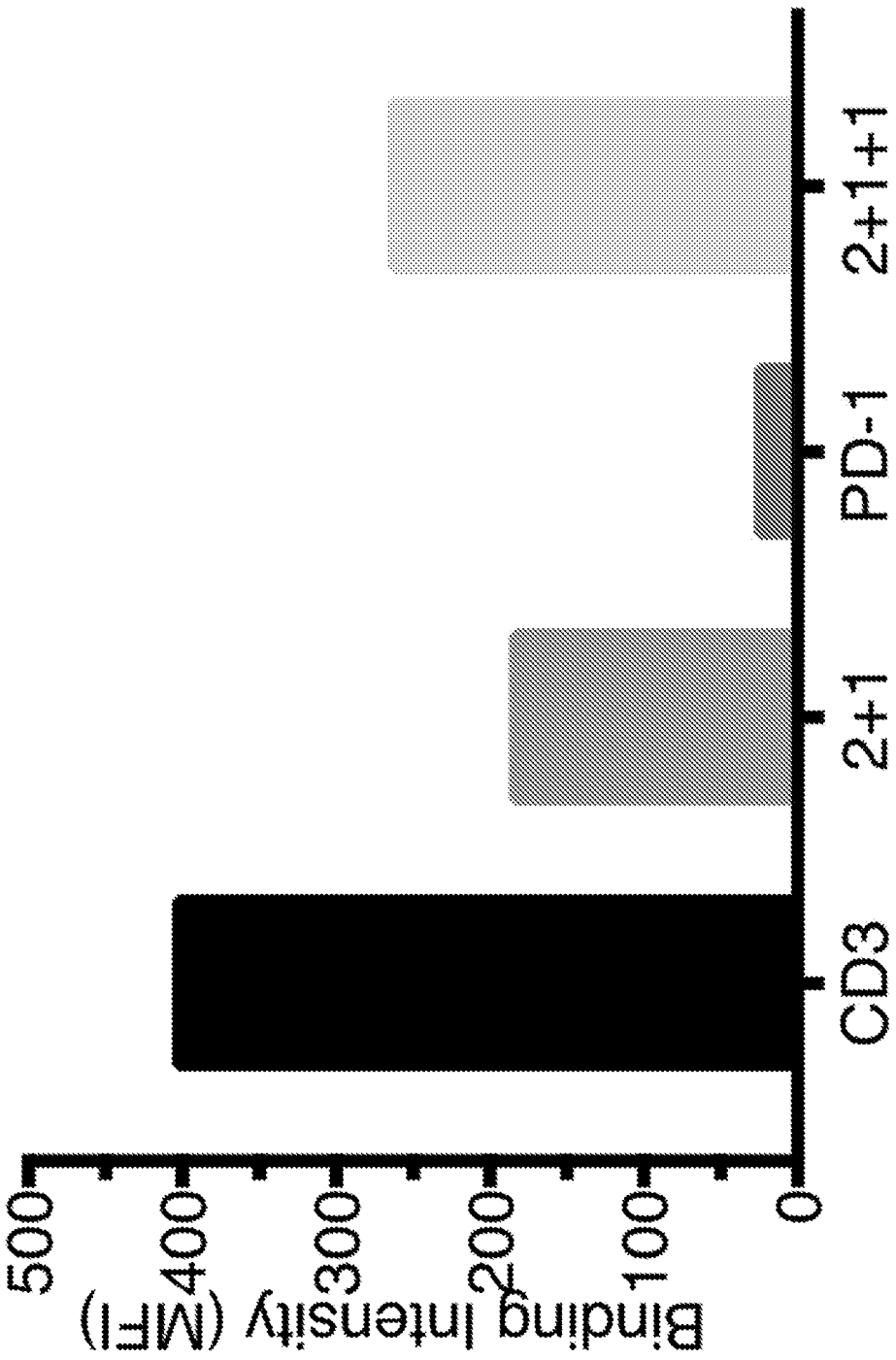

Binding Intensity (MFI)
500
400
300
200
100
0
CD3
2+1
PD-1
2+1+1
Bivalent A
Monovalent B1
Monovalent B2
3 Specificities
4 Domains
2+1+1
More Immune
Activation

Figure 21a

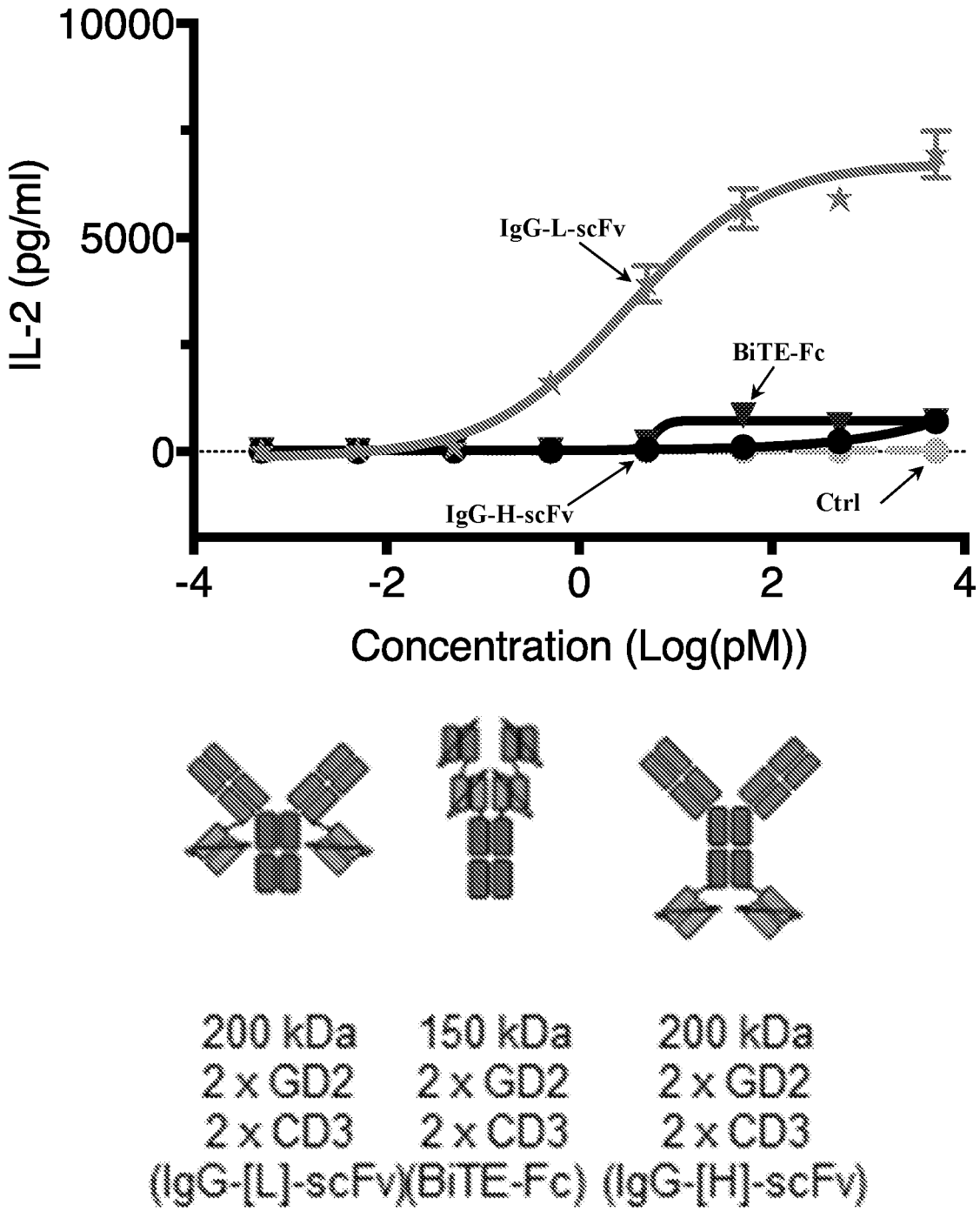

10000
5000
0
IL-2 (pg/ml)
IgG-L-scFv
BiTE-Fc
IgG-H-scFv
Ctrl
-4
-2
0
2
4
Concentration (Log(pM))
200 kDa
2 x GD2
2 x CD3
(IgG-[L]-scFv)
150 kDa
2 x GD2
2 x CD3
(BiTE-Fc)
200 kDa
2 x GD2
2 x CD3
(IgG-[H]-scFv)

Figure 21b

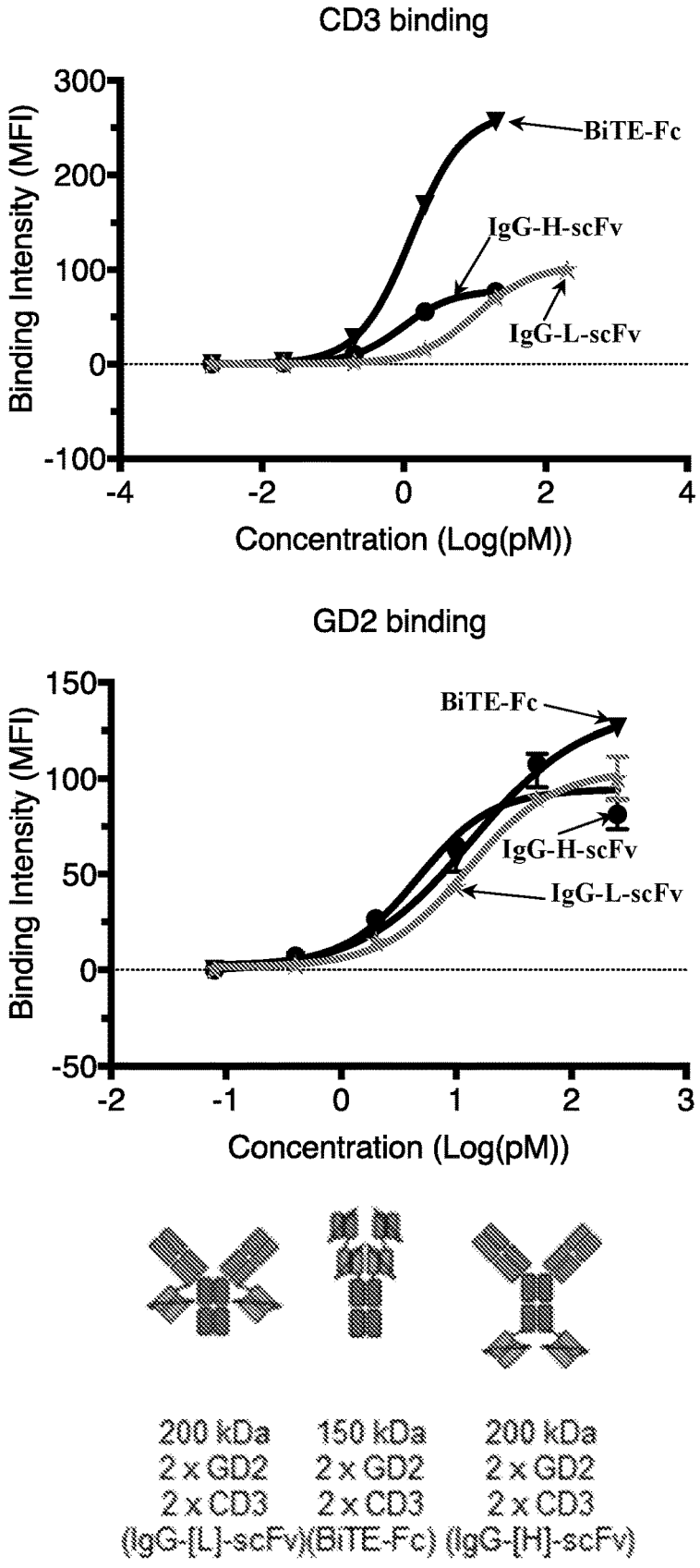

CD3 binding
Binding Intensity (MFI)
300
200
100
0
-100
-4
-2
0
2
4
Concentration (Log(pM))
BiTE-Fc
IgG-H-scFv
IgG-L-scFv
GD2 binding
Binding Intensity (MFI)
150
100
50
0
-50
-2
-1
0
1
2
3
Concentration (Log(pM))
BiTE-Fc
IgG-H-scFv
IgG-L-scFv
200 kDa
2 x GD2
2 x CD3
(IgG-[L]-scFv)
150 kDa
2 x GD2
2 x CD3
(BiTE-Fc)
200 kDa
2 x GD2
2 x CD3
(IgG-[H]-scFv)

Figure 21c

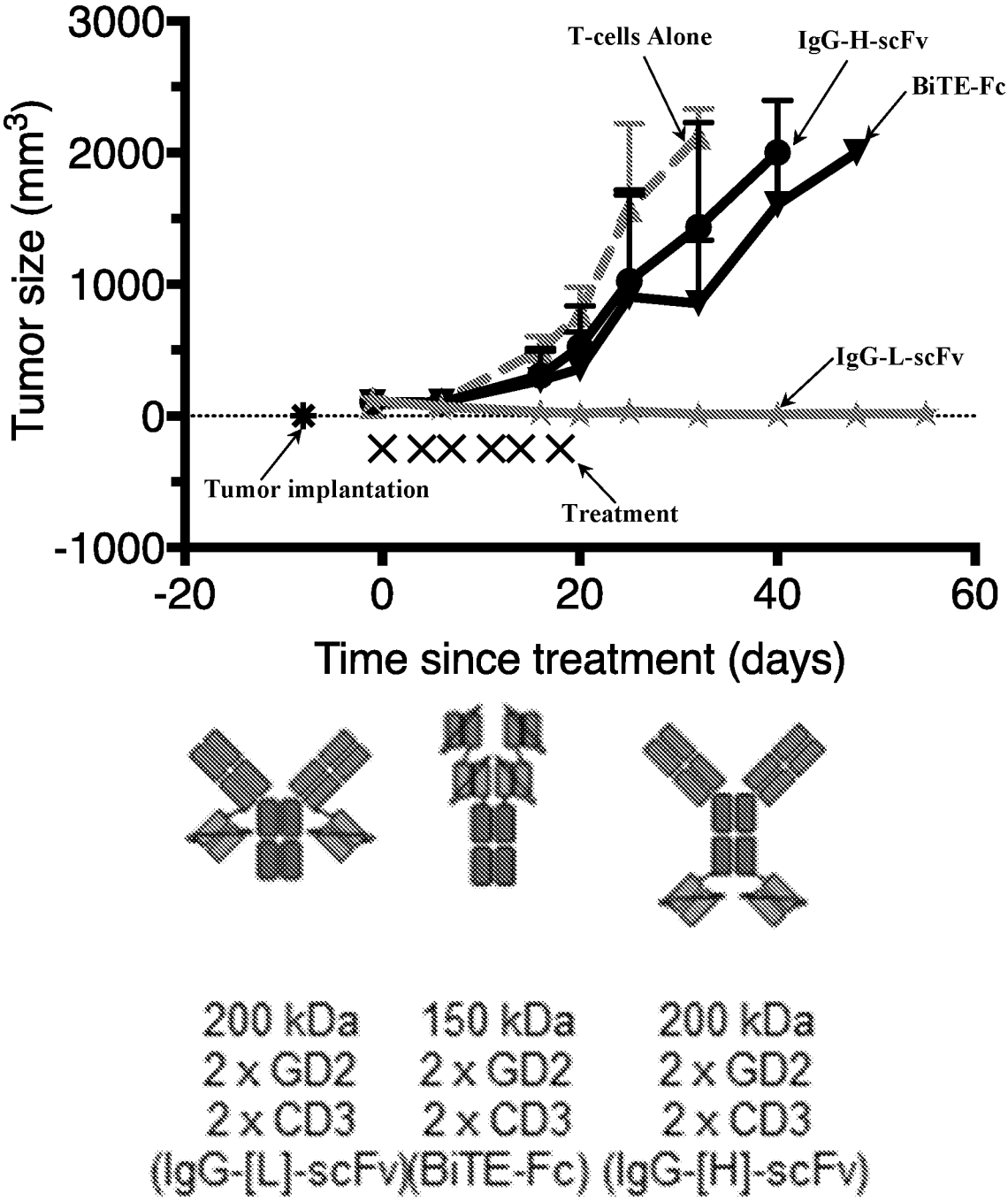

3000
2000
1000
0
-1000
Tumor size (mm3)
-20
0
20
40
60
Time since treatment (days)
T-cells Alone
IgG-H-scFv
BiTE-Fc
IgG-L-scFv
Tumor implantation
Treatment
200 kDa
2 x GD2
2 x CD3
(IgG-[L]-scFv)
150 kDa
2 x GD2
2 x CD3
(BiTE-Fc)
200 kDa
2 x GD2
2 x CD3
(IgG-[H]-scFv)

Figure 22

BsAb	EC_{50} (pM)	Fold Change	CD33 Valency	CD3 Valency	K409R mAb	F405L mAb	SEC-HPLC Purity (%)
2+2	0.9		2	2	-	-	92%
1+1H	134.4	149	1	1	IgG(huM195)	IgG(huOKT3)	94%
2+1	4.5	5	2	1	IgG(huM195)	IgG(huM195)-[L]-scFv(huOKT3)	97%
1+2	6.0	6.7	1	2	IgG(huM195)-[L]-scFv(huOKT3)	IgG(hu3F8)-[L]-scFv(huOKT3)	92%
1+1T	500	555	1	1	IgG(huM195)	IgG(hu3F8)-[L]-scFv(huOKT3)	94%
1+1C	11.5	12.3	1	1	IgG(hu3F8)	IgG(huM195)-[L]-scFv(huOKT3)	94%

Figure 23

HDTVS Type	Fab1	VH & VL SEQ ID NOs	Fab2	VH & VL SEQ ID NOs	scFv 1	VH & VL SEQ ID NOs	ScF v2	VH & VL SEQ ID NOs	Ag1	Ag2	Ag3	Ag4
2+1	hu3F8	1325 1321	hu3F8	1325 1321	huO KT3	2391 2390	-	-	GD2	GD2	CD3	-
1+1+2Lo	hu3F8	1325 1321	huM195	2395 2394	huO KT3	2391 2390	huO KT3	2391 2390	GD2	CD33	CD3	CD3
1+1+1	huM195	2395 2394	hu3F8	1325 1321	huO KT3	2391 2390	-	-	CD33	GD2	CD3	-
1+1+1	hu3F8	1325 1321	huM195	2395 2394	huO KT3	2391 2390	-	-	GD2	CD33	CD3	-
1+1+2Hi	hu3F8	1325 1321	hu4D5	1425 1421	huO KT3	2391 2390	huO KT3	2391 2390	GD2	HER2	CD3	CD3
1+1+2Hi	hu4D5	1425 1421	huM195	2395 2394	huO KT3	2391 2390	huO KT3	2391 2390	HER2	CD33	CD3	CD3
2+1	huM195	2395 2394	huM195	2395 2394	huO KT3	2391 2390	-	-	CD33	CD33	CD3	-
1+1+2Lo	hu3F8	1325 1321	hu4D5H 91A	1421 1417	huO KT3	2391 2390	huO KT3	2391 2390	GD2	HER2	CD3	CD3
1+1+2Lo	ch14.18	1309 1305	hu4D5H 91A	1421 1417	huO KT3	2391 2390	huO KT3	2391 2390	GD2	HER2	CD3	CD3
1+1+2Lo	hu4D5 H91A	1421 1417	huM195	2395 2394	huO KT3	2391 2390	huO KT3	2391 2390	HER2	CD33	CD3	CD3
1+1+2Hi	hu4D5	1425 1421	huA33	2393 2392	huO KT3	2391 2390	huO KT3	2391 2390	HER2	A33	CD3	CD3
1+1+2Lo	hu3F8	1325 1321	hu8H9	621 617	huO KT3	2391 2390	huO KT3	2391 2390	GD2	B7H3	CD3	CD3
1+1+2Lo	huM195	2395 2394	hu8H9	621 617	huO KT3	2391 2390	huO KT3	725 721	CD33	B7H3	CD3	CD3
1+1+2Hi	chC225	1101 1097	hu4D5	1425 1421	huO KT3	2391 2390	huO KT3	2391 2390	EGF R	HER2	CD3	CD3
2+1+1	hu3F8	1325 1321	hu3F8	1325 1321	huO KT3	2391 2390	hu1 D6E 10	669 665	GD2	GD2	CD3	PD-1
2+1+1	hu3F8	1325 1321	hu3F8	1325 1321	huO KT3	2391 2390	huM AB9 928	245 241	GD2	GD2	CD3	CTL A4

HDTVS Type	Fab1	VH & VL SEQ ID NOs	Fab2	VH & VL SEQ ID NOs	scFv 1	VH & VL SEQ ID NOs	ScF v2	VH & VL SEQ ID NOs	Ag1	Ag2	Ag3	Ag4
2+1+1	hu3F8	1325 1321	hu3F8	1325 1321	huOKT3	2391 2390	TNX-355	893 889	GD2	GD2	CD3	CD4
2+1+1	hu3F8	1325 1321	hu3F8	1325 1321	huOKT3	2391 2390	TGN1412	1901 1897	GD2	GD2	CD3	CD28

Figure 23 (contd.)

HETERODIMERIC TETRAVALENCY AND SPECIFICITY ANTIBODY COMPOSITIONS AND USES THEREOF

CROSS-REFERENCE TO RELATED PATENT APPLICATIONS

[0001] This application is a U.S. National Stage Application under 35 U.S.C. § 371 of International Patent Application No. PCT/US2019/063854, filed on Nov. 29, 2019, which claims the benefit of and priority to US Provisional Appl. Nos. 62/774,111, filed Nov. 30, 2018, and 62/794,523, filed Jan. 18, 2019, the disclosure of each of which are incorporated by reference herein in its entirety.

SEQUENCE LISTING

[0002] 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 Dec. 23, 2019, is named 115872-0497 SL.txt and is 1,200,059 bytes in size.

TECHNICAL FIELD

[0003] The present technology relates generally to the preparation of heterodimeric trivalent/tetravalent multispecific antibodies that specifically bind three or four distinct target antigens, and their uses. The heterodimeric trivalent/tetravalent multispecific antibodies described herein are useful in methods for detecting and treating cancer in a subject in need thereof.

BACKGROUND

[0004] The following description of the background of the present technology is provided simply as an aid in understanding the present technology and is not admitted to describe or constitute prior art to the present technology.

[0005] Many antibody platforms exist, including heterodimeric IgG and BiTE. See Spiess et al., *Mol Immunol* 67:95-106 (2015); Shima et al., *N Engl J Med* 374:2044-2053 (2016); Topp et al., *Lancet Oncol* 16:57-66 (2015). However, no single antibody platform to date has shown a clear and significant functional advantage over others within the clinic.

[0006] In the case of multispecific antibodies that engage immune cells, such as BiTEs, the ideal structure that maximizes anti-tumor activity has not been defined, and likely varies based on the target antigens or the parental antibodies (Wu & Cheung, *Pharmacology & Therapeutics* 182:161-175 (2018). Important properties may include antigen size and proximity to the cell membrane as well as serum half-life. See Bluemel et al., *Cancer Immunol Immunother* 59:1197-1209 (2010); Suzuki et al., *J Immunol* 184:1968-1976 (2010); Yang et al., *Cancer Res* 64:6673-6678 (2004). Even less is understood about the spatial orientation imparted by the antibody on the cell-to-cell interface, the strength of each individual specificity interaction, or the number of interactions. Moreover, the size of the antibody format, the flexibility of each binding domain, and their relative orientations to one another may influence the capacity to properly or effectively engage multiple antigens at once. Given these different complexities, it is of paramount importance to understand if a given platform design is properly optimized for therapeutic function.

Summary of the Present Technology

[0007] In one aspect, the present disclosure provides a heterodimeric multispecific antibody comprising a first polypeptide chain, a second polypeptide chain, a third polypeptide chain and a fourth polypeptide chain, wherein the first and second polypeptide chains are covalently bonded to one another, the second and third polypeptide chains are covalently bonded to one another, and the third and fourth polypeptide chain, and wherein: (a) the first polypeptide chain comprises in the N-terminal to C-terminal direction: (i) a light chain variable domain of a first immunoglobulin (VL-1) that is capable of specifically binding to a first epitope; (ii) a light chain constant domain of the first immunoglobulin (CL-1); (iii) a flexible peptide linker comprising the amino acid sequence $(GGGGS)_3$ (SEQ ID NO: 2506); and (iv) a light chain variable domain of a second immunoglobulin (VL-2) that is linked to a complementary heavy chain variable domain of the second immunoglobulin (VH-2), or a heavy chain variable domain of a second immunoglobulin (VH-2) that is linked to a complementary light chain variable domain of the second immunoglobulin (VL-2), wherein VL-2 and VH-2 are capable of specifically binding to a second epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ (SEQ ID NO: 2507) to form a single-chain variable fragment; (b) the second polypeptide comprises in the N-terminal to C-terminal direction: (i) a heavy chain variable domain of the first immunoglobulin (VH-1) that is capable of specifically binding to the first epitope; (ii) a first CH1 domain of the first immunoglobulin (CH1-1); and (iii) a first heterodimerization domain of the first immunoglobulin, wherein the first heterodimerization domain is incapable of forming a stable homodimer with another first heterodimerization domain; (c) the third polypeptide comprises in the N-terminal to C-terminal direction: (i) a heavy chain variable domain of a third immunoglobulin (VH-3) that is capable of specifically binding to a third epitope; (ii) a second CH1 domain of the third immunoglobulin (CH1-3); and (iii) a second heterodimerization domain of the third immunoglobulin, wherein the second heterodimerization domain comprises an amino acid sequence or a nucleic acid sequence that is distinct from the first heterodimerization domain of the first immunoglobulin, wherein the second heterodimerization domain is incapable of forming a stable homodimer with another second heterodimerization domain, and wherein the second heterodimerization domain of the third immunoglobulin is configured to form a heterodimer with the first heterodimerization domain of the first immunoglobulin; (d) the fourth polypeptide comprises in the N-terminal to C-terminal direction: (i) a light chain variable domain of the third immunoglobulin (VL-3) that is capable of specifically binding to the third epitope; (ii) a light chain constant domain of the third immunoglobulin (CL-3); (iii) a flexible peptide linker comprising the amino acid sequence $(GGGGS)_3$ (SEQ ID NO: 2506); and (iv) a light chain variable domain of a fourth immunoglobulin (VL-4) that is linked to a complementary heavy chain variable domain of the fourth immunoglobulin (VH-4), or a heavy chain variable domain of a fourth immunoglobulin (VH-4) that is linked to a complementary light chain variable domain of the fourth immunoglobulin (VL-4), wherein VL-4 and VH-4 are capable of specifically binding to the second epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ (SEQ ID NO: 2507) to

form a single-chain variable fragment, and wherein each of VL-1 and VL-3 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_L amino acid sequence selected from any one of SEQ ID NOs: 1, 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 105, 113, 121, 129, 145, 153, 161, 169, 177, 193, 201, 233, 241, 257, 273, 281, 289, 297, 305, 313, 321, 329, 337, 345, 353, 361, 369, 377, 385, 393, 401, 409, 417, 425, 433, 441, 449, 457, 465, 481, 489, 497, 521, 529, 537, 545, 553, 561, 609, 617, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 777, 785, 793, 801, 809, 817, 825, 833, 841, 849, 857, 865, 873, 881, 889, 945, 953, 961, 977, 985, 993, 1001, 1009, 1017, 1025, 1033, 1041, 1049, 1065, 1073, 1081, 1089, 1097, 1105, 1113, 1121, 1129, 1137, 1145, 1153, 1161, 1169, 1177, 1185, 1193, 1201, 1209, 1217, 1225, 1233, 1241, 1249, 1257, 1265, 1273, 1281, 1289, 1297, 1305, 1313, 1321, 1329, 1337, 1345, 1353, 1361, 1369, 1377, 1385, 1393, 1401, 1409, 1417, 1425, 1433, 1441, 1449, 1457, 1465, 1473, 1481, 1489, 1497, 1505, 1513, 1521, 1529, 1545, 1553, 1561, 1569, 1577, 1585, 1593, 1601, 1609, 1617, 1625, 1633, 1649, 1657, 1673, 1681, 1689, 1697, 1705, 1713, 1721, 1729, 1737, 1745, 1753, 1761, 1769, 1777, 1785, 1793, 1801, 1809, 1817, 1833, 1841, 1849, 1857, 1865, 1873, 1881, 1889, 1913, 1937, 1945, 1953, 1961, 1969, 1977, 1985, 1993, 2001, 2009, 2017, 2025, 2033, 2041, 2049, 2057, 2065, 2073, 2081, 2089, 2097, 2105, 2113, 2121, 2129, 2137, 2145, 2153, 2161, 2169, 2177, 2185, 2193, 2201, 2209, 2217, 2225, 2233, 2241, 2249, 2257, 2265, 2273, 2281, 2297, 2305, 2313, 2321, 2329, 2337 and 2345; and/or wherein each of VH-1 and VH-3 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_H amino acid sequence selected from any one of SEQ ID NOs: 5, 13, 21, 29, 37, 45, 53, 61, 69, 77, 85, 93, 101, 109, 117, 125, 133, 149, 157, 165, 173, 181, 197, 205, 237, 245, 261, 277, 285, 293, 301, 309, 317, 325, 333, 341, 349, 357, 365, 373, 381, 389, 397, 405, 413, 421, 429, 437, 445, 453, 461, 469, 485, 493, 501, 525, 533, 541, 549, 557, 565, 613, 621, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 781, 789, 797, 805, 813, 821, 829, 837, 845, 853, 861, 869, 877, 885, 893, 949, 957, 965, 981, 989, 997, 1005, 1013, 1021, 1029, 1037, 1045, 1053, 1069, 1077, 1085, 1093, 1101, 1109, 1117, 1125, 1133, 1141, 1149, 1157, 1165, 1173, 1181, 1189, 1197, 1205, 1213, 1221, 1229, 1237, 1245, 1253, 1261, 1269, 1277, 1285, 1293, 1301, 1309, 1317, 1325, 1333, 1341, 1349, 1357, 1365, 1373, 1381, 1389, 1397, 1405, 1413, 1421, 1429, 1437, 1445, 1453, 1461, 1469, 1477, 1485, 1493, 1501, 1509, 1517, 1525, 1533, 1549, 1557, 1565, 1573, 1581, 1589, 1597, 1605, 1613, 1621, 1629, 1637, 1653, 1661, 1677, 1685, 1693, 1701, 1709, 1717, 1725, 1733, 1741, 1749, 1757, 1765, 1773, 1781, 1789, 1797, 1805, 1813, 1821, 1837, 1845, 1853, 1861, 1869, 1877, 1885, 1893, 1917, 1941, 1949, 1957, 1965, 1973, 1981, 1989, 1997, 2005, 2013, 2021, 2029, 2037, 2045, 2053, 2061, 2069, 2077, 2085, 2093, 2101, 2109, 2117, 2125, 2133, 2141, 2149, 2157, 2165, 2173, 2181, 2189, 2197, 2205, 2213, 2221, 2229, 2237, 2245, 2253, 2261, 2269, 2277, 2285, 2301, 2309, 2317, 2325, 2333, 2341, and 2349.

[0008] In one aspect, the present disclosure provides a heterodimeric multispecific antibody comprising a first polypeptide chain, a second polypeptide chain, a third polypeptide chain and a fourth polypeptide chain, wherein the first and second polypeptide chains are covalently bonded to one another, the second and third polypeptide chains are covalently bonded to one another, and the third and fourth polypeptide chain, and wherein: (a) the first polypeptide chain comprises in the N-terminal to C-terminal direction: (i) a light chain variable domain of a first immunoglobulin (VL-1) that is capable of specifically binding to a first epitope; (ii) a light chain constant domain of the first immunoglobulin (CL-1); (iii) a flexible peptide linker comprising the amino acid sequence $(GGGGS)_3$ (SEQ ID NO: 2506); and (iv) a light chain variable domain of a second immunoglobulin (VL-2) that is linked to a complementary heavy chain variable domain of the second immunoglobulin (VH-2), or a heavy chain variable domain of a second immunoglobulin (VH-2) that is linked to a complementary light chain variable domain of the second immunoglobulin (VL-2), wherein the VL-2 and VH-2 are capable of specifically binding to a second epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ (SEQ ID NO: 2507) to form a single-chain variable fragment; (b) the second polypeptide comprises in the N-terminal to C-terminal direction: (i) a heavy chain variable domain of the first immunoglobulin (VH-1) that is capable of specifically binding to the first epitope; (ii) a first CH1 domain of the first immunoglobulin (CH1-1); and (iii) a first heterodimerization domain of the first immunoglobulin, wherein the first heterodimerization domain is incapable of forming a stable homodimer with another first heterodimerization domain; (c) the third polypeptide comprises in the N-terminal to C-terminal direction: (i) a heavy chain variable domain of a third immunoglobulin (VH-3) that is capable of specifically binding to the first epitope; (ii) a second CH1 domain of the third immunoglobulin (CH1-3); and (iii) a second heterodimerization domain of the third immunoglobulin, wherein the second heterodimerization domain comprises an amino acid sequence or a nucleic acid sequence that is distinct from the first heterodimerization domain of the first immunoglobulin, wherein the second heterodimerization domain is incapable of forming a stable homodimer with another second heterodimerization domain, and wherein the second heterodimerization domain of the third immunoglobulin is configured to form a heterodimer with the first heterodimerization domain of the first immunoglobulin; (d) the fourth polypeptide comprises in the N-terminal to C-terminal direction: (i) a light chain variable domain of the third immunoglobulin (VL-3) that is capable of specifically binding to the first epitope; (ii) a light chain constant domain of the third immunoglobulin (CL-3); (iii) a flexible peptide linker comprising the amino acid sequence $(GGGGS)_3$ (SEQ ID NO: 2506); and (iv) a light chain variable domain of a fourth immunoglobulin (VL-4) that is linked to a complementary heavy chain variable domain of the fourth immunoglobulin (VH-4), or a heavy chain variable domain of a fourth immunoglobulin (VH-4) that is linked to a complementary light chain variable domain of the fourth immunoglobulin (VL-4), wherein the VL-4 and VH-4 are capable of specifically binding to a third epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ (SEQ ID NO: 2507) to form a single-chain variable fragment, and wherein each of VL-2 and VL-4 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_L amino acid sequence selected from any one of SEQ ID NOs: 17, 25, 33, 41, 121, 137, 169, 177, 185, 193, 201, 209, 217, 225, 233, 241, 249, 257, 265, 321, 329, 337, 393, 401,

409, 473, 481, 489, 497, 505, 513, 545, 553, 561, 569, 577, 585, 593, 601, 625, 633, 641, 649, 657, 665, 673, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 785, 793, 801, 809, 817, 849, 857, 865, 873, 881, 889, 897, 905, 913, 921, 929, 937, 945, 969, 977, 1009, 1057, 1537, 1569, 1601, 1641, 1665, 1825, 1865, 1897, 1905, 1913, 1921, 1929, 2265, 2281 2289, 2329, and 2345; and/or wherein each of VH-2 and VH-4 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_H amino acid sequence selected from any one of SEQ ID NOs: 21, 29, 37, 45, 125, 141, 173, 181, 189, 197, 205, 213, 221, 229, 237, 245, 253, 261, 269, 325, 333, 341, 397, 405, 413, 477, 485, 493, 501, 509, 517, 549, 557, 565, 573, 581, 589, 597, 605, 629, 637, 645, 653, 661, 669, 677, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 789, 797, 805, 813, 821, 853, 861, 869, 877, 885, 893, 901, 909, 917, 925, 933, 941, 949, 973, 981, 1013, 1061, 1541, 1573, 1605, 1645, 1669, 1829, 1869, 1901, 1909, 1917, 1925, 1933, 2269, 2285, 2293, 2333, and 2349.

[0009] In another aspect, the present disclosure provides a heterodimeric multispecific antibody comprising a first polypeptide chain, a second polypeptide chain, a third polypeptide chain and a fourth polypeptide chain, wherein the first and second polypeptide chains are covalently bonded to one another, the second and third polypeptide chains are covalently bonded to one another, and the third and fourth polypeptide chain, and wherein: (a) the first polypeptide chain comprises in the N-terminal to C-terminal direction: (i) a light chain variable domain of a first immunoglobulin (VL-1) that is capable of specifically binding to a first epitope; (ii) a light chain constant domain of the first immunoglobulin (CL-1); (iii) a flexible peptide linker comprising the amino acid sequence $(GGGGS)_3$ (SEQ ID NO: 2506); and (iv) a light chain variable domain of a second immunoglobulin (VL-2) that is linked to a complementary heavy chain variable domain of the second immunoglobulin (VH-2), or a heavy chain variable domain of a second immunoglobulin (VH-2) that is linked to a complementary light chain variable domain of the second immunoglobulin (VL-2), wherein VL-2 and VH-2 are capable of specifically binding to a second epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ (SEQ ID NO: 2507) to form a single-chain variable fragment; (b) the second polypeptide comprises in the N-terminal to C-terminal direction: (i) a heavy chain variable domain of the first immunoglobulin (VH-1) that is capable of specifically binding to the first epitope; (ii) a first CH1 domain of the first immunoglobulin (CH1-1); and (iii) a first heterodimerization domain of the first immunoglobulin, wherein the first heterodimerization domain is incapable of forming a stable homodimer with another first heterodimerization domain; (c) the third polypeptide comprises in the N-terminal to C-terminal direction: (i) a heavy chain variable domain of a third immunoglobulin (VH-3) that is capable of specifically binding to a third epitope; (ii) a second CH1 domain of the third immunoglobulin (CH1-3); and (iii) a second heterodimerization domain of the third immunoglobulin, wherein the second heterodimerization domain comprises an amino acid sequence or a nucleic acid sequence that is distinct from the first heterodimerization domain of the first immunoglobulin, wherein the second heterodimerization domain is incapable of forming a stable homodimer with another second heterodimerization domain, and wherein the second heterodimerization domain of the third immunoglobulin is configured to form a heterodimer with the first heterodimerization domain of the first immunoglobulin; (d) the fourth polypeptide comprises in the N-terminal to C-terminal direction: (i) a light chain variable domain of the third immunoglobulin (VL-3) that is capable of specifically binding to the third epitope; (ii) a light chain constant domain of the third immunoglobulin (CL-3); (iii) a flexible peptide linker comprising the amino acid sequence $(GGGGS)_3$ (SEQ ID NO: 2506); and (iv) a light chain variable domain of a fourth immunoglobulin (VL-4) that is linked to a complementary heavy chain variable domain of the fourth immunoglobulin (VH-4), or a heavy chain variable domain of a fourth immunoglobulin (VH-4) that is linked to a complementary light chain variable domain of the fourth immunoglobulin (VL-4), wherein VL-4 and VH-4 are capable of specifically binding to the fourth epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ (SEQ ID NO: 2507) to form a single-chain variable fragment; and wherein each of VL-1 and VL-3 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_L amino acid sequence selected from any one of SEQ ID NOs: 1, 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 105, 113, 121, 129, 145, 153, 161, 169, 177, 193, 201, 233, 241, 257, 273, 281, 289, 297, 305, 313, 321, 329, 337, 345, 353, 361, 369, 377, 385, 393, 401, 409, 417, 425, 433, 441, 449, 457, 465, 481, 489, 497, 521, 529, 537, 545, 553, 561, 609, 617, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 777, 785, 793, 801, 809, 817, 825, 833, 841, 849, 857, 865, 873, 881, 889, 945, 953, 961, 977, 985, 993, 1001, 1009, 1017, 1025, 1033, 1041, 1049, 1065, 1073, 1081, 1089, 1097, 1105, 1113, 1121, 1129, 1137, 1145, 1153, 1161, 1169, 1177, 1185, 1193, 1201, 1209, 1217, 1225, 1233, 1241, 1249, 1257, 1265, 1273, 1281, 1289, 1297, 1305, 1313, 1321, 1329, 1337, 1345, 1353, 1361, 1369, 1377, 1385, 1393, 1401, 1409, 1417, 1425, 1433, 1441, 1449, 1457, 1465, 1473, 1481, 1489, 1497, 1505, 1513, 1521, 1529, 1545, 1553, 1561, 1569, 1577, 1585, 1593, 1601, 1609, 1617, 1625, 1633, 1649, 1657, 1673, 1681, 1689, 1697, 1705, 1713, 1721, 1729, 1737, 1745, 1753, 1761, 1769, 1777, 1785, 1793, 1801, 1809, 1817, 1833, 1841, 1849, 1857, 1865, 1873, 1881, 1889, 1913, 1937, 1945, 1953, 1961, 1969, 1977, 1985, 1993, 2001, 2009, 2017, 2025, 2033, 2041, 2049, 2057, 2065, 2073, 2081, 2089, 2097, 2105, 2113, 2121, 2129, 2137, 2145, 2153, 2161, 2169, 2177, 2185, 2193, 2201, 2209, 2217, 2225, 2233, 2241, 2249, 2257, 2265, 2273, 2281, 2297, 2305, 2313, 2321, 2329, 2337 and 2345; 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1413, 1421, 1429, 1437, 1445, 1453, 1461, 1469, 1477, 1485, 1493, 1501, 1509, 1517, 1525, 1533, 1549, 1557, 1565, 1573, 1581, 1589, 1597, 1605, 1613, 1621, 1629, 1637, 1653, 1661, 1677, 1685, 1693, 1701, 1709, 1717, 1725, 1733, 1741, 1749, 1757, 1765, 1773, 1781, 1789, 1797, 1805, 1813, 1821, 1837, 1845, 1853, 1861, 1869, 1877, 1885, 1893, 1917, 1941, 1949, 1957, 1965, 1973, 1981, 1989, 1997, 2005, 2013, 2021, 2029, 2037, 2045, 2053, 2061, 2069, 2077, 2085, 2093, 2101, 2109, 2117, 2125, 2133, 2141, 2149, 2157, 2165, 2173, 2181, 2189, 2197, 2205, 2213, 2221, 2229, 2237, 2245, 2253, 2261, 2269, 2277, 2285, 2301, 2309, 2317, 2325, 2333, 2341, and 2349; and/or wherein each of VL-2 and VL-4 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_L amino acid sequence selected from any one of SEQ ID NOs: 17, 25, 33, 41, 121, 137, 169, 177, 185, 193, 201, 209, 217, 225, 233, 241, 249, 257, 265, 321, 329, 337, 393, 401, 409, 473, 481, 489, 497, 505, 513, 545, 553, 561, 569, 577, 585, 593, 601, 625, 633, 641, 649, 657, 665, 673, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 785, 793, 801, 809, 817, 849, 857, 865, 873, 881, 889, 897, 905, 913, 921, 929, 937, 945, 969, 977, 1009, 1057, 1537, 1569, 1601, 1641, 1665, 1825, 1865, 1897, 1905, 1913, 1921, 1929, 2265, 2281 2289, 2329, and 2345; and/or wherein each of VH-2 and VH-4 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_H amino acid sequence selected from any one of SEQ ID NOs: 21, 29, 37, 45, 125, 141, 173, 181, 189, 197, 205, 213, 221, 229, 237, 245, 253, 261, 269, 325, 333, 341, 397, 405, 413, 477, 485, 493, 501, 509, 517, 549, 557, 565, 573, 581, 589, 597, 605, 629, 637, 645, 653, 661, 669, 677, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 789, 797, 805, 813, 821, 853, 861, 869, 877, 885, 893, 901, 909, 917, 925, 933, 941, 949, 973, 981, 1013, 1061, 1541, 1573, 1605, 1645, 1669, 1829, 1869, 1901, 1909, 1917, 1925, 1933, 2269, 2285, 2293, 2333, and 2349.

[0010] In another aspect, the present disclosure provides a heterodimeric multispecific antibody comprising a first polypeptide chain, a second polypeptide chain, a third polypeptide chain and a fourth polypeptide chain, wherein the first and second polypeptide chains are covalently bonded to one another, the second and third polypeptide chains are covalently bonded to one another, and the third and fourth polypeptide chain, and wherein: (a) the first polypeptide chain comprises in the N-terminal to C-terminal direction: (i) a light chain variable domain of a first immunoglobulin (VL-1) that is capable of specifically binding to a first epitope; (ii) a light chain constant domain of the first immunoglobulin (CL-1); (iii) a flexible peptide linker comprising the amino acid sequence $(GGGGS)_3$ (SEQ ID NO: 2506); and (iv) a light chain variable domain of a second immunoglobulin (VL-2) that is linked to a complementary heavy chain variable domain of the second immunoglobulin (VH-2), or a heavy chain variable domain of a second immunoglobulin (VH-2) that is linked to a complementary light chain variable domain of the second immunoglobulin (VL-2), wherein VL-2 and VH-2 are capable of specifically binding to a second epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ (SEQ ID NO: 2507) to form a single-chain variable fragment; (b) the second polypeptide comprises in the N-terminal to C-terminal direction: (i) a heavy chain variable domain of the first immunoglobulin (VH-1) that is capable of specifically binding to the first epitope; (ii) a first CH1 domain of the first immunoglobulin (CH1-1); and (iii) a first heterodimerization domain of the first immunoglobulin, wherein the first heterodimerization domain is incapable of forming a stable homodimer with another first heterodimerization domain; (c) the third polypeptide comprises in the N-terminal to C-terminal direction: (i) a heavy chain variable domain of a third immunoglobulin (VH-3) that is capable of specifically binding to the first epitope; (ii) a second CH1 domain of the third immunoglobulin (CH1-3); and (iii) a second heterodimerization domain of the third immunoglobulin, wherein the second heterodimerization domain comprises an amino acid sequence or a nucleic acid sequence that is distinct from the first heterodimerization domain of the first immunoglobulin, wherein the second heterodimerization domain is incapable of forming a stable homodimer with another second heterodimerization domain, and wherein the second heterodimerization domain of the third immunoglobulin is configured to form a heterodimer with the first heterodimerization domain of the first immunoglobulin; (d) the fourth polypeptide comprises in the N-terminal to C-terminal direction: (i) a light chain variable domain of the third immunoglobulin (VL-3) that is capable of specifically binding to the first epitope; and (ii) a light chain constant domain of the third immunoglobulin (CL-3); and wherein VL-2 comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_L amino acid sequence selected from any one of SEQ ID NOs: 17, 25, 33, 41, 121, 137, 169, 177, 185, 193, 201, 209, 217, 225, 233, 241, 249, 257, 265, 321, 329, 337, 393, 401, 409, 473, 481, 489, 497, 505, 513, 545, 553, 561, 569, 577, 585, 593, 601, 625, 633, 641, 649, 657, 665, 673, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 785, 793, 801, 809, 817, 849, 857, 865, 873, 881, 889, 897, 905, 913, 921, 929, 937, 945, 969, 977, 1009, 1057, 1537, 1569, 1601, 1641, 1665, 1825, 1865, 1897, 1905, 1913, 1921, 1929, 2265, 2281 2289, 2329, and 2345; and/or wherein VH-2 comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_H amino acid sequence selected from any one of SEQ ID NOs: 21, 29, 37, 45, 125, 141, 173, 181, 189, 197, 205, 213, 221, 229, 237, 245, 253, 261, 269, 325, 333, 341, 397, 405, 413, 477, 485, 493, 501, 509, 517, 549, 557, 565, 573, 581, 589, 597, 605, 629, 637, 645, 653, 661, 669, 677, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 789, 797, 805, 813, 821, 853, 861, 869, 877, 885, 893, 901, 909, 917, 925, 933, 941, 949, 973, 981, 1013, 1061, 1541, 1573, 1605, 1645, 1669, 1829, 1869, 1901, 1909, 1917, 1925, 1933, 2269, 2285, 2293, 2333, and 2349. In some embodiments, both VH-1 and VH-3 comprise the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_H amino acid sequence selected from any one of SEQ ID NOs: 5, 13, 21, 29, 37, 45, 53, 61, 69, 77, 85, 93, 101, 109, 117, 125, 133, 149, 157, 165, 173, 181, 197, 205, 237, 245, 261, 277, 285, 293, 301, 309, 317, 325, 333, 341, 349, 357, 365, 373, 381, 389, 397, 405, 413, 421, 429, 437, 445, 453, 461, 469, 485, 493, 501, 525, 533, 541, 549, 557, 565, 613, 621, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 781, 789, 797, 805, 813, 821, 829, 837, 845, 853, 861, 869, 877, 885, 893, 949, 957, 965, 981, 989, 997, 1005, 1013, 1021, 1029, 1037, 1045, 1053, 1069, 1077, 1085, 1093, 1101, 1109, 1117, 1125, 1133, 1141, 1149, 1157, 1165, 1173, 1181, 1189, 1197, 1205, 1213, 1221, 1229, 1237, 1245, 1253, 1261, 1269, 1277, 1285, 1293, 1301, 1309, 1317, 1325, 1333, 1341, 1349, 1357, 1365, 1373, 1381, 1389, 1397, 1405, 1413, 1421, 1429, 1437, 1445,

1453, 1461, 1469, 1477, 1485, 1493, 1501, 1509, 1517, 1525, 1533, 1549, 1557, 1565, 1573, 1581, 1589, 1597, 1605, 1613, 1621, 1629, 1637, 1653, 1661, 1677, 1685, 1693, 1701, 1709, 1717, 1725, 1733, 1741, 1749, 1757, 1765, 1773, 1781, 1789, 1797, 1805, 1813, 1821, 1837, 1845, 1853, 1861, 1869, 1877, 1885, 1893, 1917, 1941, 1949, 1957, 1965, 1973, 1981, 1989, 1997, 2005, 2013, 2021, 2029, 2037, 2045, 2053, 2061, 2069, 2077, 2085, 2093, 2101, 2109, 2117, 2125, 2133, 2141, 2149, 2157, 2165, 2173, 2181, 2189, 2197, 2205, 2213, 2221, 2229, 2237, 2245, 2253, 2261, 2269, 2277, 2285, 2301, 2309, 2317, 2325, 2333, 2341, and 2349; and/or both VL-1 and VL-3 comprise the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_L amino acid sequence selected from any one of SEQ ID NOs: 1, 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 105, 113, 121, 129, 145, 153, 161, 169, 177, 193, 201, 233, 241, 257, 273, 281, 289, 297, 305, 313, 321, 329, 337, 345, 353, 361, 369, 377, 385, 393, 401, 409, 417, 425, 433, 441, 449, 457, 465, 481, 489, 497, 521, 529, 537, 545, 553, 561, 609, 617, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 777, 785, 793, 801, 809, 817, 825, 833, 841, 849, 857, 865, 873, 881, 889, 945, 953, 961, 977, 985, 993, 1001, 1009, 1017, 1025, 1033, 1041, 1049, 1065, 1073, 1081, 1089, 1097, 1105, 1113, 1121, 1129, 1137, 1145, 1153, 1161, 1169, 1177, 1185, 1193, 1201, 1209, 1217, 1225, 1233, 1241, 1249, 1257, 1265, 1273, 1281, 1289, 1297, 1305, 1313, 1321, 1329, 1337, 1345, 1353, 1361, 1369, 1377, 1385, 1393, 1401, 1409, 1417, 1425, 1433, 1441, 1449, 1457, 1465, 1473, 1481, 1489, 1497, 1505, 1513, 1521, 1529, 1545, 1553, 1561, 1569, 1577, 1585, 1593, 1601, 1609, 1617, 1625, 1633, 1649, 1657, 1673, 1681, 1689, 1697, 1705, 1713, 1721, 1729, 1737, 1745, 1753, 1761, 1769, 1777, 1785, 1793, 1801, 1809, 1817, 1833, 1841, 1849, 1857, 1865, 1873, 1881, 1889, 1913, 1937, 1945, 1953, 1961, 1969, 1977, 1985, 1993, 2001, 2009, 2017, 2025, 2033, 2041, 2049, 2057, 2065, 2073, 2081, 2089, 2097, 2105, 2113, 2121, 2129, 2137, 2145, 2153, 2161, 2169, 2177, 2185, 2193, 2201, 2209, 2217, 2225, 2233, 2241, 2249, 2257, 2265, 2273, 2281, 2297, 2305, 2313, 2321, 2329, 2337 and 2345.

[0011] In yet another aspect, the present disclosure provides a heterodimeric multispecific antibody comprising a first polypeptide chain, a second polypeptide chain, a third polypeptide chain and a fourth polypeptide chain, wherein the first and second polypeptide chains are covalently bonded to one another, the second and third polypeptide chains are covalently bonded to one another, and the third and fourth polypeptide chain, and wherein: (a) the first polypeptide chain comprises in the N-terminal to C-terminal direction: (i) a light chain variable domain of a first immunoglobulin (VL-1) that is capable of specifically binding to a first epitope; (ii) a light chain constant domain of the first immunoglobulin (CL-1); (iii) a flexible peptide linker comprising the amino acid sequence $(GGGGS)_3$ (SEQ ID NO: 2506); and (iv) a light chain variable domain of a second immunoglobulin (VL-2) that is linked to a complementary heavy chain variable domain of the second immunoglobulin (VH-2), or a heavy chain variable domain of a second immunoglobulin (VH-2) that is linked to a complementary light chain variable domain of the second immunoglobulin (VL-2), wherein VL-2 and VH-2 are capable of specifically binding to a second epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ (SEQ ID NO: 2507) to form a single-chain variable fragment; (b) the second polypeptide comprises in the N-terminal to C-terminal direction: (i) a heavy chain variable domain of the first immunoglobulin (VH-1) that is capable of specifically binding to the first epitope; (ii) a first CH1 domain of the first immunoglobulin (CH1-1); and (iii) a first heterodimerization domain of the first immunoglobulin, wherein the first heterodimerization domain is incapable of forming a stable homodimer with another first heterodimerization domain; (c) the third polypeptide comprises in the N-terminal to C-terminal direction: (i) a heavy chain variable domain of a third immunoglobulin (VH-3) that is capable of specifically binding to a third epitope; (ii) a second CH1 domain of the third immunoglobulin (CH1-3); and (iii) a second heterodimerization domain of the third immunoglobulin, wherein the second heterodimerization domain comprises an amino acid sequence or a nucleic acid sequence that is distinct from the first heterodimerization domain of the first immunoglobulin, wherein the second heterodimerization domain is incapable of forming a stable homodimer with another second heterodimerization domain, and wherein the second heterodimerization domain of the third immunoglobulin is configured to form a heterodimer with the first heterodimerization domain of the first immunoglobulin; (d) the fourth polypeptide comprises in the N-terminal to C-terminal direction: (i) a light chain variable domain of the third immunoglobulin (VL-3) that is capable of specifically binding to the third epitope; and (ii) a light chain constant domain of the third immunoglobulin (CL-3); and wherein each of VL-1 and VL-3 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_L amino acid sequence selected from any one of SEQ ID NOs: 1, 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 105, 113, 121, 129, 145, 153, 161, 169, 177, 193, 201, 233, 241, 257, 273, 281, 289, 297, 305, 313, 321, 329, 337, 345, 353, 361, 369, 377, 385, 393, 401, 409, 417, 425, 433, 441, 449, 457, 465, 481, 489, 497, 521, 529, 537, 545, 553, 561, 609, 617, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 777, 785, 793, 801, 809, 817, 825, 833, 841, 849, 857, 865, 873, 881, 889, 945, 953, 961, 977, 985, 993, 1001, 1009, 1017, 1025, 1033, 1041, 1049, 1065, 1073, 1081, 1089, 1097, 1105, 1113, 1121, 1129, 1137, 1145, 1153, 1161, 1169, 1177, 1185, 1193, 1201, 1209, 1217, 1225, 1233, 1241, 1249, 1257, 1265, 1273, 1281, 1289, 1297, 1305, 1313, 1321, 1329, 1337, 1345, 1353, 1361, 1369, 1377, 1385, 1393, 1401, 1409, 1417, 1425, 1433, 1441, 1449, 1457, 1465, 1473, 1481, 1489, 1497, 1505, 1513, 1521, 1529, 1545, 1553, 1561, 1569, 1577, 1585, 1593, 1601, 1609, 1617, 1625, 1633, 1649, 1657, 1673, 1681, 1689, 1697, 1705, 1713, 1721, 1729, 1737, 1745, 1753, 1761, 1769, 1777, 1785, 1793, 1801, 1809, 1817, 1833, 1841, 1849, 1857, 1865, 1873, 1881, 1889, 1913, 1937, 1945, 1953, 1961, 1969, 1977, 1985, 1993, 2001, 2009, 2017, 2025, 2033, 2041, 2049, 2057, 2065, 2073, 2081, 2089, 2097, 2105, 2113, 2121, 2129, 2137, 2145, 2153, 2161, 2169, 2177, 2185, 2193, 2201, 2209, 2217, 2225, 2233, 2241, 2249, 2257, 2265, 2273, 2281, 2297, 2305, 2313, 2321, 2329, 2337 and 2345; and/or wherein each of VH-1 and VH-3 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_H amino acid sequence selected from any one of SEQ ID NOs: 5, 13, 21, 29, 37, 45, 53, 61, 69, 77, 85, 93, 101, 109, 117, 125, 133, 149, 157, 165, 173, 181, 197, 205, 237, 245, 261, 277, 285, 293, 301, 309, 317, 325, 333, 341, 349, 357, 365, 373, 381, 389, 397, 405, 413, 421, 429, 437, 445, 453,

461, 469, 485, 493, 501, 525, 533, 541, 549, 557, 565, 613, 621, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 781, 789, 797, 805, 813, 821, 829, 837, 845, 853, 861, 869, 877, 885, 893, 949, 957, 965, 981, 989, 997, 1005, 1013, 1021, 1029, 1037, 1045, 1053, 1069, 1077, 1085, 1093, 1101, 1109, 1117, 1125, 1133, 1141, 1149, 1157, 1165, 1173, 1181, 1189, 1197, 1205, 1213, 1221, 1229, 1237, 1245, 1253, 1261, 1269, 1277, 1285, 1293, 1301, 1309, 1317, 1325, 1333, 1341, 1349, 1357, 1365, 1373, 1381, 1389, 1397, 1405, 1413, 1421, 1429, 1437, 1445, 1453, 1461, 1469, 1477, 1485, 1493, 1501, 1509, 1517, 1525, 1533, 1549, 1557, 1565, 1573, 1581, 1589, 1597, 1605, 1613, 1621, 1629, 1637, 1653, 1661, 1677, 1685, 1693, 1701, 1709, 1717, 1725, 1733, 1741, 1749, 1757, 1765, 1773, 1781, 1789, 1797, 1805, 1813, 1821, 1837, 1845, 1853, 1861, 1869, 1877, 1885, 1893, 1917, 1941, 1949, 1957, 1965, 1973, 1981, 1989, 1997, 2005, 2013, 2021, 2029, 2037, 2045, 2053, 2061, 2069, 2077, 2085, 2093, 2101, 2109, 2117, 2125, 2133, 2141, 2149, 2157, 2165, 2173, 2181, 2189, 2197, 2205, 2213, 2221, 2229, 2237, 2245, 2253, 2261, 2269, 2277, 2285, 2301, 2309, 2317, 2325, 2333, 2341, and 2349; and/or wherein VL-2 comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_L amino acid sequence selected from any one of SEQ ID NOs: 17, 25, 33, 41, 121, 137, 169, 177, 185, 193, 201, 209, 217, 225, 233, 241, 249, 257, 265, 321, 329, 337, 393, 401, 409, 473, 481, 489, 497, 505, 513, 545, 553, 561, 569, 577, 585, 593, 601, 625, 633, 641, 649, 657, 665, 673, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 785, 793, 801, 809, 817, 849, 857, 865, 873, 881, 889, 897, 905, 913, 921, 929, 937, 945, 969, 977, 1009, 1057, 1537, 1569, 1601, 1641, 1665, 1825, 1865, 1897, 1905, 1913, 1921, 1929, 2265, 2281 2289, 2329, and 2345; and/or wherein VH-2 comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_H amino acid sequence selected from any one of SEQ ID NOs: 21, 29, 37, 45, 125, 141, 173, 181, 189, 197, 205, 213, 221, 229, 237, 245, 253, 261, 269, 325, 333, 341, 397, 405, 413, 477, 485, 493, 501, 509, 517, 549, 557, 565, 573, 581, 589, 597, 605, 629, 637, 645, 653, 661, 669, 677, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 789, 797, 805, 813, 821, 853, 861, 869, 877, 885, 893, 901, 909, 917, 925, 933, 941, 949, 973, 981, 1013, 1061, 1541, 1573, 1605, 1645, 1669, 1829, 1869, 1901, 1909, 1917, 1925, 1933, 2269, 2285, 2293, 2333, and 2349.

[0012] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, VH-1 or VH-3 comprises an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 99% or 100% identical to a V_H amino acid sequence selected from any one of SEQ ID NOs: 5, 13, 21, 29, 37, 45, 53, 61, 69, 77, 85, 93, 101, 109, 117, 125, 133, 149, 157, 165, 173, 181, 197, 205, 237, 245, 261, 277, 285, 293, 301, 309, 317, 325, 333, 341, 349, 357, 365, 373, 381, 389, 397, 405, 413, 421, 429, 437, 445, 453, 461, 469, 485, 493, 501, 525, 533, 541, 549, 557, 565, 613, 621, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 781, 789, 797, 805, 813, 821, 829, 837, 845, 853, 861, 869, 877, 885, 893, 949, 957, 965, 981, 989, 997, 1005, 1013, 1021, 1029, 1037, 1045, 1053, 1069, 1077, 1085, 1093, 1101, 1109, 1117, 1125, 1133, 1141, 1149, 1157, 1165, 1173, 1181, 1189, 1197, 1205, 1213, 1221, 1229, 1237, 1245, 1253, 1261, 1269, 1277, 1285, 1293, 1301, 1309, 1317, 1325, 1333, 1341, 1349, 1357, 1365, 1373, 1381, 1389, 1397, 1405, 1413, 1421, 1429, 1437, 1445, 1453, 1461, 1469, 1477, 1485, 1493, 1501, 1509, 1517, 1525, 1533, 1549, 1557, 1565, 1573, 1581, 1589, 1597, 1605, 1613, 1621, 1629, 1637, 1653, 1661, 1677, 1685, 1693, 1701, 1709, 1717, 1725, 1733, 1741, 1749, 1757, 1765, 1773, 1781, 1789, 1797, 1805, 1813, 1821, 1837, 1845, 1853, 1861, 1869, 1877, 1885, 1893, 1917, 1941, 1949, 1957, 1965, 1973, 1981, 1989, 1997, 2005, 2013, 2021, 2029, 2037, 2045, 2053, 2061, 2069, 2077, 2085, 2093, 2101, 2109, 2117, 2125, 2133, 2141, 2149, 2157, 2165, 2173, 2181, 2189, 2197, 2205, 2213, 2221, 2229, 2237, 2245, 2253, 2261, 2269, 2277, 2285, 2301, 2309, 2317, 2325, 2333, 2341, and 2349; and/or the VL-1 or VL-3 comprises an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 99% or 100% identical to a V_L amino acid sequence selected from any one of SEQ ID NOs: 1, 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 105, 113, 121, 129, 145, 153, 161, 169, 177, 193, 201, 233, 241, 257, 273, 281, 289, 297, 305, 313, 321, 329, 337, 345, 353, 361, 369, 377, 385, 393, 401, 409, 417, 425, 433, 441, 449, 457, 465, 481, 489, 497, 521, 529, 537, 545, 553, 561, 609, 617, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 777, 785, 793, 801, 809, 817, 825, 833, 841, 849, 857, 865, 873, 881, 889, 945, 953, 961, 977, 985, 993, 1001, 1009, 1017, 1025, 1033, 1041, 1049, 1065, 1073, 1081, 1089, 1097, 1105, 1113, 1121, 1129, 1137, 1145, 1153, 1161, 1169, 1177, 1185, 1193, 1201, 1209, 1217, 1225, 1233, 1241, 1249, 1257, 1265, 1273, 1281, 1289, 1297, 1305, 1313, 1321, 1329, 1337, 1345, 1353, 1361, 1369, 1377, 1385, 1393, 1401, 1409, 1417, 1425, 1433, 1441, 1449, 1457, 1465, 1473, 1481, 1489, 1497, 1505, 1513, 1521, 1529, 1545, 1553, 1561, 1569, 1577, 1585, 1593, 1601, 1609, 1617, 1625, 1633, 1649, 1657, 1673, 1681, 1689, 1697, 1705, 1713, 1721, 1729, 1737, 1745, 1753, 1761, 1769, 1777, 1785, 1793, 1801, 1809, 1817, 1833, 1841, 1849, 1857, 1865, 1873, 1881, 1889, 1913, 1937, 1945, 1953, 1961, 1969, 1977, 1985, 1993, 2001, 2009, 2017, 2025, 2033, 2041, 2049, 2057, 2065, 2073, 2081, 2089, 2097, 2105, 2113, 2121, 2129, 2137, 2145, 2153, 2161, 2169, 2177, 2185, 2193, 2201, 2209, 2217, 2225, 2233, 2241, 2249, 2257, 2265, 2273, 2281, 2297, 2305, 2313, 2321, 2329, 2337 and 2345.

[0013] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, VH-2 or VH-4 comprises an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 99% or 100% identical to a V_H amino acid sequence selected from any one of SEQ ID NOs: 21, 29, 37, 45, 125, 141, 173, 181, 189, 197, 205, 213, 221, 229, 237, 245, 253, 261, 269, 325, 333, 341, 397, 405, 413, 477, 485, 493, 501, 509, 517, 549, 557, 565, 573, 581, 589, 597, 605, 629, 637, 645, 653, 661, 669, 677, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 789, 797, 805, 813, 821, 853, 861, 869, 877, 885, 893, 901, 909, 917, 925, 933, 941, 949, 973, 981, 1013, 1061, 1541, 1573, 1605, 1645, 1669, 1829, 1869, 1901, 1909, 1917, 1925, 1933, 2269, 2285, 2293, 2333, and 2349; and/or VL-2 or VL-4 comprises an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or 100% identical to a VL amino acid sequence selected from any one of SEQ ID NOs: 17, 25, 33, 41, 121, 137, 169, 177, 185, 193, 201, 209, 217, 225, 233, 241, 249, 257, 265, 321, 329, 337, 393, 401, 409, 473, 481, 489, 497, 505, 513, 545, 553, 561, 569, 577, 585, 593, 601, 625, 633, 641, 649, 657, 665, 673, 681, 689,

697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 785, 793, 801, 809, 817, 849, 857, 865, 873, 881, 889, 897, 905, 913, 921, 929, 937, 945, 969, 977, 1009, 1057, 1537, 1569, 1601, 1641, 1665, 1825, 1865, 1897, 1905, 1913, 1921, 1929, 2265, 2281 2289, 2329, and 2345.

[0014] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, each of VL-1 and VH-1 comprise a V_L amino acid sequence and a V_H amino acid sequence selected from the group consisting of SEQ ID NOs: 1 and 5 respectively; SEQ ID NOs: 9 and 13 respectively; SEQ ID NOs: 17 and 21 respectively; SEQ ID NOs: 25 and 29 respectively; SEQ ID NOs: 33 and 37 respectively; SEQ ID NOs: 41 and 45 respectively; SEQ ID NOs: 49 and 53 respectively; SEQ ID NOs: 57 and 61 respectively; SEQ ID NOs: 73 and 77 respectively; SEQ ID NOs: 89 and 93 respectively; SEQ ID NOs: 97 and 101 respectively; SEQ ID NOs: 105 and 109 respectively; SEQ ID NOs: 113 and 117 respectively; SEQ ID NOs: 121 and 125 respectively; SEQ ID NOs: 129 and 133 respectively; SEQ ID NOs: 145 and 149 respectively; SEQ ID NOs: 161 and 165 respectively; SEQ ID NOs: 169 and 173 respectively; SEQ ID NOs: 177 and 181 respectively; SEQ ID NOs: 193 and 197 respectively; SEQ ID NOs: 201 and 205 respectively; SEQ ID NOs: 233 and 237 respectively; SEQ ID NOs: 241 and 245 respectively; SEQ ID NOs: 257 and 261 respectively; SEQ ID NOs: 273 and 277 respectively; SEQ ID NOs: 281 and 285 respectively; SEQ ID NOs: 289 and 293 respectively; SEQ ID NOs: 297 and 301 respectively; SEQ ID NOs: 305 and 309 respectively; SEQ ID NOs: 313 and 317 respectively; SEQ ID NOs: 321 and 325 respectively; SEQ ID NOs: 329 and 333 respectively; SEQ ID NOs: 337 and 341 respectively; SEQ ID NOs: 345 and 349 respectively; SEQ ID NOs: 353 and 357 respectively; SEQ ID NOs: 361 and 365 respectively; SEQ ID NOs: 369 and 373 respectively; SEQ ID NOs: 377 and 381 respectively; SEQ ID NOs: 385 and 389 respectively; SEQ ID NOs: 393 and 397 respectively; SEQ ID NOs: 401 and 405 respectively; SEQ ID NOs: 409 and 413 respectively; SEQ ID NOs: 417 and 421 respectively; SEQ ID NOs: 425 and 429 respectively; SEQ ID NOs: 433 and 437 respectively; SEQ ID NOs: 441 and 445 respectively; SEQ ID NOs: 449 and 453 respectively; SEQ ID NOs: 457 and 461 respectively; SEQ ID NOs: 465 and 469 respectively; SEQ ID NOs: 481 and 485 respectively; SEQ ID NOs: 489 and 493 respectively; SEQ ID NOs: 497 and 501 respectively; SEQ ID NOs: 521 and 525 respectively; SEQ ID NOs: 529 and 533 respectively; SEQ ID NOs: 537 and 541 respectively; SEQ ID NOs: 545 and 549 respectively; SEQ ID NOs: 553 and 557 respectively; SEQ ID NOs: 561 and 565 respectively; SEQ ID NOs: 609 and 613 respectively; SEQ ID NOs: 617 and 621 respectively; SEQ ID NOs: 681 and 685 respectively; SEQ ID NOs: 689 and 693 respectively; SEQ ID NOs: 697 and 701 respectively; SEQ ID NOs: 705 and 709 respectively; SEQ ID NOs: 713 and 717 respectively; SEQ ID NOs: 721 and 725 respectively; SEQ ID NOs: 729 and 733 respectively; SEQ ID NOs: 737 and 741 respectively; SEQ ID NOs: 745 and 749 respectively; SEQ ID NOs: 753 and 757 respectively; SEQ ID NOs: 761 and 765 respectively; SEQ ID NOs: 769 and 773 respectively; SEQ ID NOs: 785 and 789 respectively; SEQ ID NOs: 793 and 797 respectively; SEQ ID NOs: 801 and 805 respectively; SEQ ID NOs: 809 and 813 respectively; SEQ ID NOs: 817 and 821 respectively; SEQ ID NOs: 825 and 829 respectively; SEQ ID NOs: 833 and 837 respectively; SEQ ID NOs: 841 and 845 respectively; SEQ ID NOs: 849 and 853 respectively; SEQ ID NOs: 857 and 861 respectively; SEQ ID NOs: 865 and 869 respectively; SEQ ID NOs: 873 and 877 respectively; SEQ ID NOs: 881 and 885 respectively; SEQ ID NOs: 889 and 893 respectively; SEQ ID NOs: 945 and 949 respectively; SEQ ID NOs: 953 and 957 respectively; SEQ ID NOs: 961 and 965 respectively; SEQ ID NOs: 977 and 981 respectively; SEQ ID NOs: 985 and 989 respectively; SEQ ID NOs: 993 and 997 respectively; SEQ ID NOs: 1001 and 1005 respectively; SEQ ID NOs: 1009 and 1013 respectively; SEQ ID NOs: 1017 and 1021 respectively; SEQ ID NOs: 1025 and 1029 respectively; SEQ ID NOs: 1033 and 1037 respectively; SEQ ID NOs: 1041 and 1045 respectively; SEQ ID NOs: 1065 and 1069 respectively; SEQ ID NOs: 1073 and 1077 respectively; SEQ ID NOs: 1081 and 1085 respectively; SEQ ID NOs: 1089 and 1093 respectively; SEQ ID NOs: 1097 and 1101 respectively; SEQ ID NOs: 1113 and 1117 respectively; SEQ ID NOs: 1121 and 1125 respectively; SEQ ID NOs: 1129 and 1133 respectively; SEQ ID NOs: 1137 and 1141 respectively; SEQ ID NOs: 1145 and 1149 respectively; SEQ ID NOs: 1153 and 1157 respectively; SEQ ID NOs: 1161 and 1165 respectively; SEQ ID NOs: 1169 and 1173 respectively; SEQ ID NOs: 1185 and 1189 respectively; SEQ ID NOs: 1193 and 1197 respectively; SEQ ID NOs: 1201 and 1205 respectively; SEQ ID NOs: 1209 and 1213 respectively; SEQ ID NOs: 1217 and 1221 respectively; SEQ ID NOs: 1225 and 1229 respectively; SEQ ID NOs: 1233 and 1237 respectively; SEQ ID NOs: 1241 and 1245 respectively; SEQ ID NOs: 1249 and 1253 respectively; SEQ ID NOs: 1257 and 1261 respectively; SEQ ID NOs: 1265 and 1269 respectively; SEQ ID NOs: 1273 and 1277 respectively; SEQ ID NOs: 1281 and 1285 respectively; SEQ ID NOs: 1289 and 1293 respectively; SEQ ID NOs: 1297 and 1301 respectively; 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SEQ ID NOs: 1649 and 1653 respectively; SEQ ID NOs: 1657 and 1661 respectively; SEQ ID NOs: 1673 and 1677 respectively; SEQ ID NOs: 1681 and 1685 respectively; SEQ ID NOs: 1689 and 1693 respectively; SEQ ID NOs: 1697 and 1701 respectively; SEQ ID NOs: 1705 and 1709 respectively; SEQ ID NOs: 1713 and 1717 respectively; SEQ ID NOs: 1721 and 1725 respectively; SEQ ID NOs: 1729 and 1733 respectively; SEQ ID NOs: 1737 and 1741 respectively; SEQ ID NOs: 1745 and 1749 respectively; SEQ ID NOs: 1753 and 1757 respectively; SEQ ID NOs: 1761 and 1765 respectively; SEQ ID NOs: 1769 and 1773 respectively; SEQ ID NOs: 1777 and 1781 respectively; SEQ ID NOs: 1785 and 1789 respectively; SEQ ID NOs: 1793 and 1797 respectively; SEQ ID NOs: 1801 and 1805 respectively; SEQ ID NOs: 1809 and 1813 respectively; SEQ ID NOs: 1817 and 1821 respectively; SEQ ID NOs: 1833 and 1837 respectively; SEQ ID NOs: 1841 and 1845 respectively; SEQ ID NOs: 1849 and 1853 respectively; SEQ ID NOs: 1857 and 1861 respectively; SEQ ID NOs: 1865 and 1869 respectively; SEQ ID NOs: 1873 and 1877 respectively; SEQ ID NOs: 1881 and 1885 respectively; SEQ ID NOs: 1889 and 1893 respectively; SEQ ID NOs: 1913 and 1917 respectively; SEQ ID NOs: 1937 and 1941 respectively; SEQ ID NOs: 1945 and 1949 respectively; SEQ ID NOs: 1953 and 1957 respectively; SEQ ID NOs: 1961 and 1965 respectively; SEQ ID NOs: 1969 and 1973 respectively; SEQ ID NOs: 1977 and 1981 respectively; SEQ ID NOs: 1985 and 1989 respectively; SEQ ID NOs: 1993 and 1997 respectively; SEQ ID NOs: 2001 and 2005 respectively; SEQ ID NOs: 2009 and 2013 respectively; SEQ ID NOs: 2017 and 2021 respectively; SEQ ID NOs: 2025 and 2029 respectively; SEQ ID NOs: 2033 and 2037 respectively; SEQ ID NOs: 2041 and 2045 respectively; SEQ ID NOs: 2049 and 2053 respectively; SEQ ID NOs: 2057 and 2061 respectively; SEQ ID NOs: 2065 and 2069 respectively; SEQ ID NOs: 2073 and 2077 respectively; SEQ ID NOs: 2081 and 2085 respectively; SEQ ID NOs: 2089 and 2093 respectively; SEQ ID NOs: 2097 and 2101 respectively; SEQ ID NOs: 2105 and 2109 respectively; SEQ ID NOs: 2113 and 2117 respectively; SEQ ID NOs: 2121 and 2125 respectively; SEQ ID NOs: 2129 and 2133 respectively; SEQ ID NOs: 2137 and 2141 respectively; SEQ ID NOs: 2145 and 2149 respectively; SEQ ID NOs: 2153 and 2157 respectively; SEQ ID NOs: 2161 and 2165 respectively; SEQ ID NOs: 2169 and 2173 respectively; SEQ ID NOs: 2177 and 2181 respectively; SEQ ID NOs: 2185 and 2189 respectively; SEQ ID NOs: 2193 and 2197 respectively; SEQ ID NOs: 2201 and 2205 respectively; SEQ ID NOs: 2209 and 2213 respectively; SEQ ID NOs: 2217 and 2221 respectively; SEQ ID NOs: 2225 and 2229 respectively; SEQ ID NOs: 2233 and 2237 respectively; SEQ ID NOs: 2241 and 2245 respectively; SEQ ID NOs: 2249 and 2253 respectively; SEQ ID NOs: 2257 and 2261 respectively; SEQ ID NOs: 2273 and 2277 respectively; SEQ ID NOs: 2281 and 2285 respectively; SEQ ID NOs: 2305 and 2309 respectively; SEQ ID NOs: 2313 and 2317 respectively; SEQ ID NOs: 2321 and 2325 respectively; SEQ ID NOs: 2329 and 2333 respectively; SEQ ID NOs: 2337 and 2341 respectively; and SEQ ID NOs: 2345 and 2349 respectively.

[0015] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, each of VL-3 and VH-3 comprise a V_L amino acid sequence and a V_H amino acid sequence selected from the group consisting of SEQ ID NOs: 1 and 5 respectively; SEQ ID NOs: 9 and 13 respectively; SEQ ID NOs: 17 and 21 respectively; SEQ ID NOs: 25 and 29 respectively; SEQ ID NOs: 33 and 37 respectively; SEQ ID NOs: 41 and 45 respectively; SEQ ID NOs: 49 and 53 respectively; SEQ ID NOs: 57 and 61 respectively; SEQ ID NOs: 73 and 77 respectively; SEQ ID NOs: 89 and 93 respectively; SEQ ID NOs: 97 and 101 respectively; SEQ ID NOs: 105 and 109 respectively; SEQ ID NOs: 113 and 117 respectively; SEQ ID NOs: 121 and 125 respectively; SEQ ID NOs: 129 and 133 respectively; SEQ ID NOs: 145 and 149 respectively; SEQ ID NOs: 161 and 165 respectively; SEQ ID NOs: 169 and 173 respectively; SEQ ID NOs: 177 and 181 respectively; SEQ ID NOs: 193 and 197 respectively; SEQ ID NOs: 201 and 205 respectively; SEQ ID NOs: 233 and 237 respectively; SEQ ID NOs: 241 and 245 respectively; SEQ ID NOs: 257 and 261 respectively; SEQ ID NOs: 273 and 277 respectively; SEQ ID NOs: 281 and 285 respectively; SEQ ID NOs: 289 and 293 respectively; SEQ ID NOs: 297 and 301 respectively; SEQ ID NOs: 305 and 309 respectively; SEQ ID NOs: 313 and 317 respectively; SEQ ID NOs: 321 and 325 respectively; SEQ ID NOs: 329 and 333 respectively; SEQ ID NOs: 337 and 341 respectively; SEQ ID NOs: 345 and 349 respectively; SEQ ID NOs: 353 and 357 respectively; SEQ ID NOs: 361 and 365 respectively; SEQ ID NOs: 369 and 373 respectively; SEQ ID NOs: 377 and 381 respectively; SEQ ID NOs: 385 and 389 respectively; SEQ ID NOs: 393 and 397 respectively; SEQ ID NOs: 401 and 405 respectively; SEQ ID NOs: 409 and 413 respectively; SEQ ID NOs: 417 and 421 respectively; SEQ ID NOs: 425 and 429 respectively; SEQ ID NOs: 433 and 437 respectively; SEQ ID NOs: 441 and 445 respectively; SEQ ID NOs: 449 and 453 respectively; SEQ ID NOs: 457 and 461 respectively; SEQ ID NOs: 465 and 469 respectively; SEQ ID NOs: 481 and 485 respectively; SEQ ID NOs: 489 and 493 respectively; SEQ ID NOs: 497 and 501 respectively; SEQ ID NOs: 521 and 525 respectively; SEQ ID NOs: 529 and 533 respectively; SEQ ID NOs: 537 and 541 respectively; SEQ ID NOs: 545 and 549 respectively; SEQ ID NOs: 553 and 557 respectively; SEQ ID NOs: 561 and 565 respectively; SEQ ID NOs: 609 and 613 respectively; SEQ ID NOs: 617 and 621 respectively; SEQ ID NOs: 681 and 685 respectively; SEQ ID NOs: 689 and 693 respectively; SEQ ID NOs: 697 and 701 respectively; SEQ ID NOs: 705 and 709 respectively; SEQ ID NOs: 713 and 717 respectively; SEQ ID NOs: 721 and 725 respectively; SEQ ID NOs: 729 and 733 respectively; SEQ ID NOs: 737 and 741 respectively; SEQ ID NOs: 745 and 749 respectively; SEQ ID NOs: 753 and 757 respectively; SEQ ID NOs: 761 and 765 respectively; SEQ ID NOs: 769 and 773 respectively; SEQ ID NOs: 785 and 789 respectively; SEQ ID NOs: 793 and 797 respectively; SEQ ID NOs: 801 and 805 respectively; SEQ ID NOs: 809 and 813 respectively; SEQ ID NOs: 817 and 821 respectively; SEQ ID NOs: 825 and 829 respectively; SEQ ID NOs: 833 and 837 respectively; SEQ ID NOs: 841 and 845 respectively; SEQ ID NOs: 849 and 853 respectively; SEQ ID NOs: 857 and 861 respectively; SEQ ID NOs: 865 and 869 respectively; SEQ ID NOs: 873 and 877 respectively; SEQ ID NOs: 881 and 885 respectively; SEQ ID NOs: 889 and 893 respectively; SEQ ID NOs: 945 and 949 respectively; SEQ ID NOs: 953 and 957 respectively; SEQ ID NOs: 961 and 965 respectively; SEQ ID NOs: 977 and 981 respectively; SEQ ID NOs: 985 and 989 respectively; SEQ ID NOs: 993 and 997

respectively; SEQ ID NOs: 1001 and 1005 respectively; SEQ ID NOs: 1009 and 1013 respectively; SEQ ID NOs: 1017 and 1021 respectively; SEQ ID NOs: 1025 and 1029 respectively; SEQ ID NOs: 1033 and 1037 respectively; SEQ ID NOs: 1041 and 1045 respectively; SEQ ID NOs: 1065 and 1069 respectively; SEQ ID NOs: 1073 and 1077 respectively; SEQ ID NOs: 1081 and 1085 respectively; SEQ ID NOs: 1089 and 1093 respectively; SEQ ID NOs: 1097 and 1101 respectively; SEQ ID NOs: 1113 and 1117 respectively; SEQ ID NOs: 1121 and 1125 respectively; SEQ ID NOs: 1129 and 1133 respectively; SEQ ID NOs: 1137 and 1141 respectively; SEQ ID NOs: 1145 and 1149 respectively; SEQ ID NOs: 1153 and 1157 respectively; SEQ ID NOs: 1161 and 1165 respectively; SEQ ID NOs: 1169 and 1173 respectively; SEQ ID NOs: 1185 and 1189 respectively; SEQ ID NOs: 1193 and 1197 respectively; SEQ ID NOs: 1201 and 1205 respectively; SEQ ID NOs: 1209 and 1213 respectively; SEQ ID NOs: 1217 and 1221 respectively; SEQ ID NOs: 1225 and 1229 respectively; 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SEQ ID NOs: 1881 and 1885 respectively; SEQ ID NOs: 1889 and 1893 respectively; SEQ ID NOs: 1913 and 1917 respectively; SEQ ID NOs: 1937 and 1941 respectively; SEQ ID NOs: 1945 and 1949 respectively; SEQ ID NOs: 1953 and 1957 respectively; SEQ ID NOs: 1961 and 1965 respectively; SEQ ID NOs: 1969 and 1973 respectively; SEQ ID NOs: 1977 and 1981 respectively; SEQ ID NOs: 1985 and 1989 respectively; SEQ ID NOs: 1993 and 1997 respectively; SEQ ID NOs: 2001 and 2005 respectively; SEQ ID NOs: 2009 and 2013 respectively; SEQ ID NOs: 2017 and 2021 respectively; SEQ ID NOs: 2025 and 2029 respectively; SEQ ID NOs: 2033 and 2037 respectively; SEQ ID NOs: 2041 and 2045 respectively; SEQ ID NOs: 2049 and 2053 respectively; SEQ ID NOs: 2057 and 2061 respectively; SEQ ID NOs: 2065 and 2069 respectively; SEQ ID NOs: 2073 and 2077 respectively; SEQ ID NOs: 2081 and 2085 respectively; SEQ ID NOs: 2089 and 2093 respectively; SEQ ID NOs: 2097 and 2101 respectively; SEQ ID NOs: 2105 and 2109 respectively; 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SEQ ID NOs: 2337 and 2341 respectively; and SEQ ID NOs: 2345 and 2349 respectively.

[0016] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, each of VL-1 and VH-1 comprise a V_L amino acid sequence and a V_H amino acid sequence selected from the group consisting of SEQ ID NOs: 9 and 13 respectively; SEQ ID NOs: 49 and 53 respectively; SEQ ID NOs: 57 and 61 respectively; SEQ ID NOs: 65 and 69 respectively; SEQ ID NOs: 81 and 85 respectively; SEQ ID NOs: 153 and 157 respectively; SEQ ID NOs: 161 and 165 respectively; SEQ ID NOs: 193 and 197 respectively; SEQ ID NOs: 201 and 205 respectively; SEQ ID NOs: 273 and 277 respectively; SEQ ID NOs: 281 and 285 respectively; SEQ ID NOs: 289 and 293 respectively; SEQ ID NOs: 297 and 301 respec-

tively; SEQ ID NOs: 305 and 309 respectively; SEQ ID NOs: 313 and 317 respectively; SEQ ID NOs: 361 and 365 respectively; SEQ ID NOs: 377 and 381 respectively; SEQ ID NOs: 393 and 397 respectively; SEQ ID NOs: 401 and 405 respectively; SEQ ID NOs: 409 and 413 respectively; SEQ ID NOs: 417 and 421 respectively; SEQ ID NOs: 425 and 429 respectively; SEQ ID NOs: 433 and 437 respectively; SEQ ID NOs: 441 and 445 respectively; SEQ ID NOs: 449 and 453 respectively; SEQ ID NOs: 457 and 461 respectively; SEQ ID NOs: 465 and 469 respectively; SEQ ID NOs: 681 and 685 respectively; SEQ ID NOs: 689 and 693 respectively; SEQ ID NOs: 697 and 701 respectively; SEQ ID NOs: 705 and 709 respectively; SEQ ID NOs: 713 and 717 respectively; SEQ ID NOs: 721 and 725 respectively; SEQ ID NOs: 737 and 741 respectively; SEQ ID NOs: 745 and 749 respectively; SEQ ID NOs: 753 and 757 respectively; SEQ ID NOs: 761 and 765 respectively; SEQ ID NOs: 777 and 781 respectively; SEQ ID NOs: 825 and 829 respectively; SEQ ID NOs: 833 and 837 respectively; SEQ ID NOs: 841 and 845 respectively; SEQ ID NOs: 953 and 957 respectively; SEQ ID NOs: 961 and 965 respectively; SEQ ID NOs: 977 and 981 respectively; SEQ ID NOs: 993 and 997 respectively; SEQ ID NOs: 1001 and 1005 respectively; SEQ ID NOs: 1009 and 1013 respectively; SEQ ID NOs: 1017 and 1021 respectively; SEQ ID NOs: 1033 and 1037 respectively; SEQ ID NOs: 1049 and 1053 respectively; SEQ ID NOs: 1073 and 1077 respectively; SEQ ID NOs: 1081 and 1085 respectively; SEQ ID NOs: 1089 and 1093 respectively; SEQ ID NOs: 1105 and 1109 respectively; SEQ ID NOs: 1129 and 1133 respectively; SEQ ID NOs: 1137 and 1141 respectively; SEQ ID NOs: 1153 and 1157 respectively; SEQ ID NOs: 1161 and 1165 respectively; SEQ ID NOs: 1177 and 1181 respectively; SEQ ID NOs: 1225 and 1229 respectively; SEQ ID NOs: 1241 and 1245 respectively; SEQ ID NOs: 1257 and 1261 respectively; SEQ ID NOs: 1265 and 1269 respectively; SEQ ID NOs: 1297 and 1301 respectively; SEQ ID NOs: 1393 and 1397 respectively; SEQ ID NOs: 1409 and 1413 respectively; SEQ ID NOs: 1425 and 1429 respectively; SEQ ID NOs: 1441 and 1445 respectively; SEQ ID NOs: 1449 and 1453 respectively; SEQ ID NOs: 1457 and 1461 respectively; SEQ ID NOs: 1465 and 1469 respectively; SEQ ID NOs: 1473 and 1477 respectively; SEQ ID NOs: 1481 and 1485 respectively; SEQ ID NOs: 1497 and 1501 respectively; SEQ ID NOs: 1505 and 1509 respectively; SEQ ID NOs: 1513 and 1517 respectively; SEQ ID NOs: 1521 and 1525 respectively; SEQ ID NOs: 1529 and 1533 respectively; SEQ ID NOs: 1545 and 1549 respectively; SEQ ID NOs: 1553 and 1557 respectively; SEQ ID NOs: 1561 and 1565 respectively; SEQ ID NOs: 1569 and 1573 respectively; SEQ ID NOs: 1577 and 1581 respectively; SEQ ID NOs: 1585 and 1589 respectively; SEQ ID NOs: 1609 and 1613 respectively; SEQ ID NOs: 1617 and 1621 respectively; SEQ ID NOs: 1649 and 1653 respectively; SEQ ID NOs: 1657 and 1661 respectively; SEQ ID NOs: 1673 and 1677 respectively; SEQ ID NOs: 1689 and 1693 respectively; SEQ ID NOs: 1697 and 1701 respectively; SEQ ID NOs: 1705 and 1709 respectively; SEQ ID NOs: 1713 and 1717 respectively; SEQ ID NOs: 1721 and 1725 respectively; SEQ ID NOs: 1729 and 1733 respectively; SEQ ID NOs: 1745 and 1749 respectively; SEQ ID NOs: 1753 and 1757 respectively; SEQ ID NOs: 1761 and 1765 respectively; SEQ ID NOs: 1769 and 1773 respectively; SEQ ID NOs: 1777 and 1781 respectively; SEQ ID NOs: 1785 and 1789 respectively; SEQ ID NOs: 1793 and 1797 respectively; SEQ ID NOs: 1817 and 1821 respectively; SEQ ID NOs: 1833 and 1837 respectively; SEQ ID NOs: 1841 and 1845 respectively; SEQ ID NOs: 1849 and 1853 respectively; SEQ ID NOs: 1857 and 1861 respectively; SEQ ID NOs: 1865 and 1869 respectively; SEQ ID NOs: 1889 and 1893 respectively; SEQ ID NOs: 2257 and 2261 respectively; SEQ ID NOs: 2265 and 2269 respectively; SEQ ID NOs: 2281 and 2285 respectively; SEQ ID NOs: 2297 and 2301 respectively; SEQ ID NOs: 2305 and 2309 respectively; SEQ ID NOs: 2313 and 2317 respectively; SEQ ID NOs: 2321 and 2325 respectively; SEQ ID NOs: 2329 and 2333 respectively; SEQ ID NOs: 2337 and 2341 respectively; and SEQ ID NOs: 2345 and 2349 respectively.

[0017] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, each of VL-3 and VH-3 comprise a V_L amino acid sequence and a V_H amino acid sequence selected from the group consisting of SEQ ID NOs: 9 and 13 respectively; SEQ ID NOs: 49 and 53 respectively; SEQ ID NOs: 57 and 61 respectively; SEQ ID NOs: 65 and 69 respectively; SEQ ID NOs: 81 and 85 respectively; SEQ ID NOs: 153 and 157 respectively; SEQ ID NOs: 161 and 165 respectively; SEQ ID NOs: 193 and 197 respectively; SEQ ID NOs: 201 and 205 respectively; SEQ ID NOs: 273 and 277 respectively; SEQ ID NOs: 281 and 285 respectively; SEQ ID NOs: 289 and 293 respectively; SEQ ID NOs: 297 and 301 respectively; SEQ ID NOs: 305 and 309 respectively; SEQ ID NOs: 313 and 317 respectively; SEQ ID NOs: 361 and 365 respectively; SEQ ID NOs: 377 and 381 respectively; SEQ ID NOs: 393 and 397 respectively; SEQ ID NOs: 401 and 405 respectively; SEQ ID NOs: 409 and 413 respectively; SEQ ID NOs: 417 and 421 respectively; SEQ ID NOs: 425 and 429 respectively; SEQ ID NOs: 433 and 437 respectively; SEQ ID NOs: 441 and 445 respectively; SEQ ID NOs: 449 and 453 respectively; SEQ ID NOs: 457 and 461 respectively; SEQ ID NOs: 465 and 469 respectively; SEQ ID NOs: 681 and 685 respectively; SEQ ID NOs: 689 and 693 respectively; SEQ ID NOs: 697 and 701 respectively; SEQ ID NOs: 705 and 709 respectively; SEQ ID NOs: 713 and 717 respectively; SEQ ID NOs: 721 and 725 respectively; SEQ ID NOs: 737 and 741 respectively; SEQ ID NOs: 745 and 749 respectively; SEQ ID NOs: 753 and 757 respectively; SEQ ID NOs: 761 and 765 respectively; SEQ ID NOs: 777 and 781 respectively; SEQ ID NOs: 825 and 829 respectively; SEQ ID NOs: 833 and 837 respectively; SEQ ID NOs: 841 and 845 respectively; SEQ ID NOs: 953 and 957 respectively; SEQ ID NOs: 961 and 965 respectively; SEQ ID NOs: 977 and 981 respectively; SEQ ID NOs: 993 and 997 respectively; SEQ ID NOs: 1001 and 1005 respectively; SEQ ID NOs: 1009 and 1013 respectively; SEQ ID NOs: 1017 and 1021 respectively; SEQ ID NOs: 1033 and 1037 respectively; SEQ ID NOs: 1049 and 1053 respectively; SEQ ID NOs: 1073 and 1077 respectively; SEQ ID NOs: 1081 and 1085 respectively; SEQ ID NOs: 1089 and 1093 respectively; SEQ ID NOs: 1105 and 1109 respectively; SEQ ID NOs: 1129 and 1133 respectively; SEQ ID NOs: 1137 and 1141 respectively; SEQ ID NOs: 1153 and 1157 respectively; SEQ ID NOs: 1161 and 1165 respectively; SEQ ID NOs: 1177 and 1181 respectively; SEQ ID NOs: 1225 and 1229 respectively; SEQ ID NOs: 1241 and 1245 respectively; SEQ ID NOs: 1257 and 1261 respectively; SEQ ID NOs: 1265 and 1269 respec-

tively; SEQ ID NOs: 1297 and 1301 respectively; SEQ ID NOs: 1393 and 1397 respectively; SEQ ID NOs: 1409 and 1413 respectively; SEQ ID NOs: 1425 and 1429 respectively; SEQ ID NOs: 1441 and 1445 respectively; SEQ ID NOs: 1449 and 1453 respectively; SEQ ID NOs: 1457 and 1461 respectively; SEQ ID NOs: 1465 and 1469 respectively; SEQ ID NOs: 1473 and 1477 respectively; SEQ ID NOs: 1481 and 1485 respectively; SEQ ID NOs: 1497 and 1501 respectively; SEQ ID NOs: 1505 and 1509 respectively; SEQ ID NOs: 1513 and 1517 respectively; SEQ ID NOs: 1521 and 1525 respectively; SEQ ID NOs: 1529 and 1533 respectively; SEQ ID NOs: 1545 and 1549 respectively; SEQ ID NOs: 1553 and 1557 respectively; SEQ ID NOs: 1561 and 1565 respectively; SEQ ID NOs: 1569 and 1573 respectively; SEQ ID NOs: 1577 and 1581 respectively; SEQ ID NOs: 1585 and 1589 respectively; SEQ ID NOs: 1609 and 1613 respectively; SEQ ID NOs: 1617 and 1621 respectively; SEQ ID NOs: 1649 and 1653 respectively; SEQ ID NOs: 1657 and 1661 respectively; SEQ ID NOs: 1673 and 1677 respectively; SEQ ID NOs: 1689 and 1693 respectively; SEQ ID NOs: 1697 and 1701 respectively; SEQ ID NOs: 1705 and 1709 respectively; SEQ ID NOs: 1713 and 1717 respectively; SEQ ID NOs: 1721 and 1725 respectively; SEQ ID NOs: 1729 and 1733 respectively; SEQ ID NOs: 1745 and 1749 respectively; SEQ ID NOs: 1753 and 1757 respectively; SEQ ID NOs: 1761 and 1765 respectively; SEQ ID NOs: 1769 and 1773 respectively; SEQ ID NOs: 1777 and 1781 respectively; SEQ ID NOs: 1785 and 1789 respectively; SEQ ID NOs: 1793 and 1797 respectively; SEQ ID NOs: 1817 and 1821 respectively; SEQ ID NOs: 1833 and 1837 respectively; SEQ ID NOs: 1841 and 1845 respectively; SEQ ID NOs: 1849 and 1853 respectively; SEQ ID NOs: 1857 and 1861 respectively; SEQ ID NOs: 1865 and 1869 respectively; SEQ ID NOs: 1889 and 1893 respectively; SEQ ID NOs: 2257 and 2261 respectively; SEQ ID NOs: 2265 and 2269 respectively; SEQ ID NOs: 2281 and 2285 respectively; SEQ ID NOs: 2297 and 2301 respectively; SEQ ID NOs: 2305 and 2309 respectively; SEQ ID NOs: 2313 and 2317 respectively; SEQ ID NOs: 2321 and 2325 respectively; SEQ ID NOs: 2329 and 2333 respectively; SEQ ID NOs: 2337 and 2341 respectively; and SEQ ID NOs: 2345 and 2349 respectively.

[0018] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, each of VL-2 and VH-2 comprise a V_L amino acid sequence and a V_H amino acid sequence selected from the group consisting of SEQ ID NOs: 17 and 21 respectively; SEQ ID NOs: 25 and 29 respectively; SEQ ID NOs: 33 and 37 respectively; SEQ ID NOs: 41 and 45 respectively; SEQ ID NOs: 121 and 125 respectively; SEQ ID NOs: 137 and 141 respectively; SEQ ID NOs: 169 and 173 respectively; SEQ ID NOs: 177 and 181 respectively; SEQ ID NOs: 185 and 189 respectively; SEQ ID NOs: 193 and 197 respectively; SEQ ID NOs: 201 and 205 respectively; SEQ ID NOs: 209 and 213 respectively; SEQ ID NOs: 217 and 221 respectively; SEQ ID NOs: 225 and 229 respectively; SEQ ID NOs: 233 and 237 respectively; SEQ ID NOs: 241 and 245 respectively; SEQ ID NOs: 249 and 253 respectively; SEQ ID NOs: 257 and 261 respectively; SEQ ID NOs: 265 and 269 respectively; SEQ ID NOs: 321 and 325 respectively; SEQ ID NOs: 329 and 333 respectively; SEQ ID NOs: 337 and 341 respectively; SEQ ID NOs: 393 and 397 respectively; SEQ ID NOs: 401 and 405 respectively; SEQ ID NOs: 409 and 413 respectively; SEQ ID NOs: 473 and 477 respectively; SEQ ID NOs: 481 and 485 respectively; SEQ ID NOs: 489 and 493 respectively; SEQ ID NOs: 497 and 501 respectively; SEQ ID NOs: 505 and 509 respectively; SEQ ID NOs: 513 and 517 respectively; SEQ ID NOs: 545 and 549 respectively; SEQ ID NOs: 553 and 557 respectively; SEQ ID NOs: 561 and 565 respectively; SEQ ID NOs: 569 and 573 respectively; SEQ ID NOs: 577 and 581 respectively; SEQ ID NOs: 585 and 589 respectively; SEQ ID NOs: 593 and 597 respectively; SEQ ID NOs: 601 and 605 respectively; SEQ ID NOs: 625 and 629 respectively; SEQ ID NOs: 633 and 637 respectively; SEQ ID NOs: 641 and 645 respectively; SEQ ID NOs: 649 and 653 respectively; SEQ ID NOs: 657 and 661 respectively; SEQ ID NOs: 665 and 669 respectively; SEQ ID NOs: 673 and 677 respectively; SEQ ID NOs: 681 and 685 respectively; SEQ ID NOs: 689 and 693 respectively; SEQ ID NOs: 697 and 701 respectively; SEQ ID NOs: 705 and 709 respectively; SEQ ID NOs: 713 and 717 respectively; SEQ ID NOs: 721 and 725 respectively; SEQ ID NOs: 729 and 733 respectively; SEQ ID NOs: 737 and 741 respectively; SEQ ID NOs: 745 and 749 respectively; SEQ ID NOs: 753 and 757 respectively; SEQ ID NOs: 761 and 765 respectively; SEQ ID NOs: 769 and 773 respectively; SEQ ID NOs: 785 and 789 respectively; SEQ ID NOs: 793 and 797 respectively; SEQ ID NOs: 801 and 805 respectively; SEQ ID NOs: 809 and 813 respectively; SEQ ID NOs: 817 and 821 respectively; SEQ ID NOs: 849 and 853 respectively; SEQ ID NOs: 857 and 861 respectively; SEQ ID NOs: 865 and 869 respectively; SEQ ID NOs: 873 and 877 respectively; SEQ ID NOs: 881 and 885 respectively; SEQ ID NOs: 889 and 893 respectively; SEQ ID NOs: 897 and 901 respectively; SEQ ID NOs: 905 and 909 respectively; SEQ ID NOs: 913 and 917 respectively; SEQ ID NOs: 921 and 925 respectively; SEQ ID NOs: 929 and 933 respectively; SEQ ID NOs: 937 and 941 respectively; SEQ ID NOs: 945 and 949 respectively; SEQ ID NOs: 969 and 973 respectively; SEQ ID NOs: 977 and 981 respectively; SEQ ID NOs: 1009 and 1013 respectively; SEQ ID NOs: 1057 and 1061 respectively; SEQ ID NOs: 1537 and 1541 respectively; SEQ ID NOs: 1569 and 1573 respectively; SEQ ID NOs: 1601 and 1605 respectively; SEQ ID NOs: 1641 and 1645 respectively; SEQ ID NOs: 1665 and 1669 respectively; SEQ ID NOs: 1825 and 1829 respectively; SEQ ID NOs: 1865 and 1869 respectively; SEQ ID NOs: 1897 and 1901 respectively; SEQ ID NOs: 1905 and 1909 respectively; SEQ ID NOs: 1913 and 1917 respectively; SEQ ID NOs: 1921 and 1925 respectively; SEQ ID NOs: 1929 and 1933 respectively; SEQ ID NOs: 2265 and 2269 respectively; SEQ ID NOs: 2281 and 2285 respectively; 2289 and 2293 respectively; 2329 and 2333 respectively; and SEQ ID NOs: 2345 and 2349, respectively.

[0019] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, each of VL-4 and VH-4 comprise a V_L amino acid sequence and a V_H amino acid sequence selected from the group consisting of SEQ ID NOs: 17 and 21 respectively; SEQ ID NOs: 25 and 29 respectively; SEQ ID NOs: 33 and 37 respectively; SEQ ID NOs: 41 and 45 respectively; SEQ ID NOs: 121 and 125 respectively; SEQ ID NOs: 137 and 141 respectively; SEQ ID NOs: 169 and 173 respectively; SEQ ID NOs: 177 and 181 respectively; SEQ ID NOs: 185 and 189 respectively; SEQ ID NOs: 193 and 197 respectively; SEQ ID NOs: 201 and 205 respectively;

SEQ ID NOs: 209 and 213 respectively; SEQ ID NOs: 217 and 221 respectively; SEQ ID NOs: 225 and 229 respectively; SEQ ID NOs: 233 and 237 respectively; SEQ ID NOs: 241 and 245 respectively; SEQ ID NOs: 249 and 253 respectively; SEQ ID NOs: 257 and 261 respectively; SEQ ID NOs: 265 and 269 respectively; SEQ ID NOs: 321 and 325 respectively; SEQ ID NOs: 329 and 333 respectively; SEQ ID NOs: 337 and 341 respectively; SEQ ID NOs: 393 and 397 respectively; SEQ ID NOs: 401 and 405 respectively; SEQ ID NOs: 409 and 413 respectively; SEQ ID NOs: 473 and 477 respectively; SEQ ID NOs: 481 and 485 respectively; SEQ ID NOs: 489 and 493 respectively; SEQ ID NOs: 497 and 501 respectively; SEQ ID NOs: 505 and 509 respectively; SEQ ID NOs: 513 and 517 respectively; SEQ ID NOs: 545 and 549 respectively; SEQ ID NOs: 553 and 557 respectively; SEQ ID NOs: 561 and 565 respectively; SEQ ID NOs: 569 and 573 respectively; SEQ ID NOs: 577 and 581 respectively; SEQ ID NOs: 585 and 589 respectively; SEQ ID NOs: 593 and 597 respectively; SEQ ID NOs: 601 and 605 respectively; SEQ ID NOs: 625 and 629 respectively; SEQ ID NOs: 633 and 637 respectively; SEQ ID NOs: 641 and 645 respectively; SEQ ID NOs: 649 and 653 respectively; SEQ ID NOs: 657 and 661 respectively; SEQ ID NOs: 665 and 669 respectively; SEQ ID NOs: 673 and 677 respectively; SEQ ID NOs: 681 and 685 respectively; SEQ ID NOs: 689 and 693 respectively; SEQ ID NOs: 697 and 701 respectively; SEQ ID NOs: 705 and 709 respectively; SEQ ID NOs: 713 and 717 respectively; SEQ ID NOs: 721 and 725 respectively; SEQ ID NOs: 729 and 733 respectively; SEQ ID NOs: 737 and 741 respectively; SEQ ID NOs: 745 and 749 respectively; SEQ ID NOs: 753 and 757 respectively; SEQ ID NOs: 761 and 765 respectively; SEQ ID NOs: 769 and 773 respectively; SEQ ID NOs: 785 and 789 respectively; SEQ ID NOs: 793 and 797 respectively; SEQ ID NOs: 801 and 805 respectively; SEQ ID NOs: 809 and 813 respectively; SEQ ID NOs: 817 and 821 respectively; SEQ ID NOs: 849 and 853 respectively; SEQ ID NOs: 857 and 861 respectively; SEQ ID NOs: 865 and 869 respectively; SEQ ID NOs: 873 and 877 respectively; SEQ ID NOs: 881 and 885 respectively; SEQ ID NOs: 889 and 893 respectively; SEQ ID NOs: 897 and 901 respectively; SEQ ID NOs: 905 and 909 respectively; SEQ ID NOs: 913 and 917 respectively; SEQ ID NOs: 921 and 925 respectively; SEQ ID NOs: 929 and 933 respectively; SEQ ID NOs: 937 and 941 respectively; SEQ ID NOs: 945 and 949 respectively; SEQ ID NOs: 969 and 973 respectively; SEQ ID NOs: 977 and 981 respectively; SEQ ID NOs: 1009 and 1013 respectively; SEQ ID NOs: 1057 and 1061 respectively; SEQ ID NOs: 1537 and 1541 respectively; SEQ ID NOs: 1569 and 1573 respectively; SEQ ID NOs: 1601 and 1605 respectively; SEQ ID NOs: 1641 and 1645 respectively; SEQ ID NOs: 1665 and 1669 respectively; SEQ ID NOs: 1825 and 1829 respectively; SEQ ID NOs: 1865 and 1869 respectively; SEQ ID NOs: 1897 and 1901 respectively; SEQ ID NOs: 1905 and 1909 respectively; SEQ ID NOs: 1913 and 1917 respectively; SEQ ID NOs: 1921 and 1925 respectively; SEQ ID NOs: 1929 and 1933 respectively; SEQ ID NOs: 2265 and 2269 respectively; SEQ ID NOs: 2281 and 2285 respectively; 2289 and 2293 respectively; 2329 and 2333 respectively; and SEQ ID NOs: 2345 and 2349, respectively.

[0020] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, the first immunoglobulin or the third immunoglobulin binds to a cell surface antigen selected from the group consisting of a2b b3 (Glycoprotein IIb/IIIa), a4, a4b7, a4b7+aEb7, a5, Activin receptor type-2B, ALK1, Alpha-synuclein, amyloid beta, APP, AXL, Blood Group A, CAIX, CCL-2, CD105 (endoglin), CD115 (CSF1R), CD116a (CSF2Ra), CD123, CD152 (CTLA4), CD184 (CXCR4), CD19, CD192 (CCR2), CD194 (CCR4), CD195 (CCR5), CD20, CD200, CD22, CD221 (IGF1R), CD248, CD25, CD257 (BAFF), CD26, CD262 (DR5), CD276 (B7H3), CD3, CD30 (TNFRSF8), CD319 (SLAMF7), CD33, CD332 (FGFR2), CD350 (FZD10), CD37, CD371 (CLEC12A), CD38, CD4, CD49b (a2), CD51 (a5), CD52, CD56, CD61 (a4b3), CD70, CD73 (NTSE), CD74, CEA, Claudin-18.2, cMET, CRLR, DLL3, DLL4, DNA/histone (H1) complex, EGFR, EpCAM, EGFR-HER3, EGFRvIII, EphA3, ERGT (GalNAc) Tn Antigen, FLT1, FOLR1, frizzled family receptor (FZD), Lewis Y, Lewis X, GCGR, GD2, GD2 α-acetyl, GD3, GM1, GM1 fucosyl, GM2, GPA33, GPNMB, GUCY2C, HER2, HER3, HGFR (cMET), IgHe, IGLF2, Kallikreins, LINGO1, LOXL2, Ly6/PLAUR domain-containing protein 3, MADCAM1, MAG, Mesothelin, MT1-MMP (MMP14), MUC1, Mucin SAC, *NaPi*2b, NeuGc-GM3, notch, NOTCH2/NOTCH3 receptors, oxLDL, P-selectin, PCSK9, PDGFRA, PDGFRa, phosphatidylserine, polysialic acid, PSMA, PVRL4, RGMA, CD240D Blood group D antigen, root plate-specific spondin 3, serum amyloid P component, STEAP-1, TACSTD2, TGFb, TWEAKR, TYRP1, VEGFR2, VSIR, CD171 (L1CAM), CD19, CD47, pMHC[NY-ESO1], pMHC[MART1], pMHC [MAGEA1], pMHC[Tyrosinase], pMHC[gp100], pMHC [MUC1], pMHC[tax], pMHC[WT-1], pMHC[EBNA-1], pMHC[LMP2], pMHC[hTERT], GPC3, CD80, CD23, and fibronectin extra domain-B. The first immunoglobulin and the third immunoglobulin may bind to the same epitope on a target cell or two different epitopes on a target cell. In some embodiments, the target cell is a cancer cell.

[0021] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, the second immunoglobulin or the fourth immunoglobulin bind to an epitope on a white blood cell, a monocyte, a lymphocyte, a granulocyte, a macrophage, a T cell, a NK cell, a B cell, a NKT cell, an ILC, or neutrophil.

[0022] In any of the above embodiments of the heterodimeric multispecific antibodies disclosed herein, the second immunoglobulin or the fourth immunoglobulin bind to an antigen selected from the group consisting of Dabigatran, a4, a4b7, a4b7+aEb7, a5, AXL, BnDOTA, CD11a (LFA-1), CD3, CD4, CD8, CD16, CD19, CD22, CD23, CD25, CD28, CD30 (TNFRSF8), CD33, CD38, CD40, CD40L, CD47, CD49b (a2), CD54 (ICAM-1), CD56, CD74, CD80, CD115 (CSF1R), CD116a (CSF2Ra), CD123, CD134 (OX40), CD137 (41BB), CD152 (CTLA4), CD184 (CXCR4), CD192 (CCR2), CD194 (CCR4), CD195 (CCR5), CD223 (LAG-3), CD252 (OX40L), CD254 (RANKL), CD262 (DR5), CD27, CD200, CD221 (IGF1R), CD248, CD274 (PD-L1), CD275 (ICOS-L), CD278 (ICOS), CD279 (PD-1), CD319 (SLAMF7), CD371 (CLEC12A), MADCAM1, MT1-MMP (MMP14), NKG2A, NRP1,TIGIT, VSIR, KIRDL1/2/3, and KIR2DL2. The second immunoglobulin and the fourth immunoglobulin may bind to the same epitope or different epitopes on a white blood cell, a monocyte, a lymphocyte, a granulocyte, a macrophage, a T cell, a NK cell, a B cell, a NKT cell, an ILC, or neutrophil. In some embodiments, the second immunoglobulin binds CD3

and the fourth immunoglobulin binds an immune cell receptor selected from the group consisting of CD4, CD8, CD25, CD28, CTLA4, OX40, ICOS, PD-1, PD-L1, 41BB, CD2, CD69, and CD45. In other embodiments, the second immunoglobulin binds CD16 and the fourth immunoglobulin binds an immune cell receptor selected from the group consisting of CD56, NKG2D, and KIRDL1/2/3. In certain embodiments, the fourth immunoglobulin binds to an agent selected from the group consisting of a cytokine, a nucleic acid, a hapten, a small molecule, a radionuclide, an immunotoxin, a vitamin, a peptide, a lipid, a carbohydrate, biotin, digoxin, or any conjugated variants thereof.

[0023] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, the first immunoglobulin and the third immunoglobulin bind to their respective epitopes with a monovalent affinity or an effective affinity between about 100 nM to about 100 pM. In certain embodiments, the first immunoglobulin and the third immunoglobulin bind to cell surface epitopes that are between 60 and 120 angstroms apart.

[0024] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, the first immunoglobulin and the third immunoglobulin bind to their respective epitopes with a monovalent affinity or an effective affinity that is less than 100 pM. In certain embodiments, the first immunoglobulin and the third immunoglobulin bind to cell surface epitopes that are up to 180 angstroms apart.

[0025] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, the first heterodimerization domain of the first immunoglobulin and/or the second heterodimerization domain of the third immunoglobulin is a CH2-CH3 domain and has an isotype selected from the group consisting of IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgM, IgD, and IgE.

[0026] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, the first heterodimerization domain of the first immunoglobulin and/or the second heterodimerization domain of the third immunoglobulin comprises an IgG1 constant region comprising one or more amino acid substitutions selected from the group consisting of N297A and K322A. Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, the first heterodimerization domain of the first immunoglobulin is a CH2-CH3 domain comprising a K409R mutation and the second heterodimerization domain of the third immunoglobulin is a CH2-CH3 domain comprising a F405L mutation.

[0027] Also disclosed herein are recombinant nucleic acid sequences encoding any of the antibodies described herein. In another aspect, the present technology provides a host cell or vector expressing any nucleic acid sequence encoding any of the antibodies described herein.

[0028] In any of the above embodiments of the immunoglobulin-related compositions of the present technology, the HDTVS antibody may be optionally conjugated to an agent selected from the group consisting of isotopes, dyes, chromagens, contrast agents, drugs, toxins, cytokines, enzymes, enzyme inhibitors, hormones, hormone antagonists, growth factors, radionuclides, metals, liposomes, nanoparticles, RNA, DNA or any combination thereof.

[0029] In one aspect, the present disclosure provides a method for treating cancer in a subject in need thereof, comprising administering to the subject an effective amount of a heterodimeric multispecific antibody disclosed herein. The cancer may be lung cancer, colorectal cancer, skin cancer, breast cancer, ovarian cancer, leukemia, pancreatic cancer, or gastric cancer. Additionally or alternatively, in some embodiments, the heterodimeric multispecific antibody is administered to the subject separately, sequentially or simultaneously with an additional therapeutic agent.

[0030] Also disclosed herein are kits for detection and/or treatment of a disease (e.g., cancers), comprising at least one heterodimeric trivalent/tetravalent multispecific antibody of the present technology and instructions for use.

BRIEF DESCRIPTION OF THE DRAWINGS

[0031] FIG. **1***a* shows the basic design strategy of each HeteroDimeric TetraValency and Specificity (HDTVS) variant compared with the parental 2+2 IgG-[L]-scFv. The 5 heterodimeric IgG-L-scFv designs display novel biological activities. Each construct uses heterodimerization to achieve tri- or tetraspecificity.

[0032] FIG. **1***b* shows a schematic of the 1+1+2 Low affinity design and how it can be used to distinguish single-antigen positive healthy cells from dual-antigen positive target cells. Single antigen positivity would result in inferior immune cell activation over dual antigen positivity.

[0033] FIG. **1***c* shows a schematic of the 1+1+2 High affinity design and how it can be used to target either (or both) of two different cellular antigens.

[0034] FIG. **1***d* shows a schematic of the 2+1+1 design and how it can be used to improve immune cell activation. Targeting of two different immune cell receptors can be used to more specifically recruit an immune cell population or provide greater immune cell activation or inhibition through cross linking of multiple receptors.

[0035] FIG. **1***e* shows a schematic of the 2+1+1 design and how it can be used to broaden immune cell recruitment or combine payload delivery with immunotherapy. Each HDTVS antibody needs only one immune cell receptor for recruitment and activation. The additional domain can then be used to bind payloads (for diagnostics, therapy, recruitment, etc.) or additional effector cells.

[0036] FIG. **1***f* shows a schematic of the 1+1+1+1 design and how it can be used to combine the benefits of 1+1+2 with 2+1+1. In this embodiment, tetraspecificity can bring better specificity or a broader range of targets, as well and improved immune cell activation or payload delivery.

[0037] FIG. **2***a* shows the superior cytotoxicity, binding and in vivo potency of the IgG-[L]-scFv design over the IgG-Het and BiTE formats. A 4 hr Cr^{51} release assay was used to evaluate cytotoxicity of activated T-cells against M14 melanoma tumor cells. Flow cytometry was used to evaluate differences in antigen binding of each bispecific antibody to huCD3 or GD2 on activated T cells or M14 melanoma tumor cells, respectively. Affinities were measured using SPR on GD2 coated streptavidin chips. Two mouse models were used for assessing in vivo potency, a syngeneic transgenic model which has huCD3 expressing murine T cells, and a humanized xenograft model using activated human T-cells engrafted into immunodeficient IL2-$re^{-/-}$ $Rag2^{-/-}$ BALB/c mice. Mice were implanted subcutaneously with GD2(+) tumors and treated intravenously with a particular test bispecific antibody.

[0038] FIG. **2***b* shows the superior cytotoxicity of the IgG-[L]-scFv design over the IgG-het using two additional anti-GD2 sequences.

[0039] FIG. **3** shows the schematics of 4 IgG-[L]-scFv heterodimeric variants along with the parental format and the IgG-Het format. Designs are ranked by their relative potency.

[0040] FIG. **4** shows the in vitro binding activity of the various IgG-[L]-scFv variants. GD2 and CD3 affinities were measured using SPR with GD2 or huCD3de coated chips, respectively. Cell binding was assayed by flow cytometry using activated human T cells or M14 melanoma cells. T-cell: tumor cell conjugate formation was measured by flow cytometry using differentially labeled activated human T cells and M14 melanoma tumor cells.

[0041] FIG. **5** shows the in vitro cytotoxicity of each IgG-[L]-scFv variant against two cell lines: M14 melanoma and IMR32 neuroblastoma. Cytotoxicity was measured using a 4 hr Cr^{51} release assay and activated human T-cells.

[0042] FIG. **6** shows the in vitro immune cell activation of each IgG-[L]-scFv variant. Activation was measured by flow cytometry. Naïve purified T cells and M14 melanoma cells were co-cultured for 24 or 96 hrs, harvested and stained for CD69 or CD25, respectively. T cells for the 96 hr time points were also labeled with Cell Trace Violet (CTV). Culture supernatant was also collected at the 24 hr time point for cytokine measurements.

[0043] FIG. **7** shows the in vivo activity of each IgG-[L]-scFv variant. Two mouse models were used for assessing in vivo potency, a syngeneic transgenic model which has huCD3 expressing murine T cells, and a humanized xenograft model using activated human T-cells engrafted into immunodeficient IL2-$rg^{-/-}$ $Rag2^{-/-}$ BALB/c mice. Mice were implanted subcutaneously with GD2(+) tumors and treated intravenously with a particular test bispecific antibody.

[0044] FIG. **8** shows various dual bivalent bispecific antibody formats compared to the IgG-[L]-scFv design. Cytotoxicity was evaluated using a 4 hr Cr^{51} release assay using activated human T cells and M14 melanoma cells. Conjugation activity was measured using flow cytometry. Cell binding was evaluated by flow cytometry using activated human T cells and M14 melanoma cells.

[0045] FIG. **9** shows IgG-[L]-scFv variants which bind CD33 or HER2. Cell binding activities were measured by flow cytometry using Molm13, SKMEL28, or MCF7 cells. Cytotoxicity was assessed using Molm13 cells and activated human T cells in a 4 hr Cr^{51} release assay.

[0046] FIG. **10***a* shows two 1+1+2 designs (high and low affinity variants). Cell binding and cytotoxicity assays used the GD2(+)HER2(+) cell line U2OS. Cytotoxicity was measured using 4 hr Cr^{51} release, and cell binding was evaluated using flow cytometry.

[0047] FIG. **10***b* shows two 1+1+2 designs (high and low affinity variants). Cell binding and cytotoxicity assays used the GD2(+) IMR32 neuroblastoma cells or HER2(+) HCC1954 breast cancer cells. Cytotoxicity was measured using 4 hr Cr^{51} release, and cell binding was evaluated using flow cytometry.

[0048] FIGS. **11***a*-11*e* show exemplary Fc variants that are capable of heterodimerization.

[0049] FIG. **12***a* shows various dual bivalent bispecific antibody formats compared in vivo to the IgG-[L]-scFv design. Schematics show all four dual bivalent bispecific antibodies expressed.

[0050] FIG. **12***b* shows the mean tumor growth for in vivo huDKO arming model. Tumor responses were evaluated using a T-cell arming model, where T-cells were preincubated with each BsAb for 20 min at a concentration to achieve equal anti-GD2 binding domains (as verified by flow cytometry). These prelabeled or "armed" T-cells were injected intravenously into tumor bearing DKO mice. Each line represents one BsAb. Solid black triangles represent a dose of BsAb armed human activated T-cells (huATC) and IL-2. The dotted black line represents no measurable tumor and the star represents the tumor implantation. Error bars represent standard deviation.

[0051] FIG. **12***c* shows tumor growth from individual mice. Each figure represents one treatment group, with schematics (see above) for reference. Each solid line represents a single mouse, and the dotted lines represents the group average.

[0052] FIG. **13** demonstrates the combined binding effect of L1CAM/GD2 1+1+2 Lo, a heterodimeric 1+1+2Lo format antibody that can bind ganglioside GD2 and adhesion protein L1CAM simultaneously. Design of the 1+1+2 Lo format antibody is shown on the left side. Homodimeric formats against GD2 and L1CAM were included for reference. For this binding assay, Neuroblastoma cells (IMR32) were incubated with each antibody for 30 minutes at 4° C., washed and incubated with a fluorescent anti-human secondary antibody. After the final wash, the cells were analyzed using flow cytometry. In this example, the binding of the low affinity 1+1+2 HDTVS antibody was stronger than the anti-L1CAM homodimeric antibody, but weaker than the anti-GD2 homodimeric antibody, thus showing improved targeting specificity for tumors expressing both GD2 and L1CAM.

[0053] FIG. **14** demonstrates the combined binding effect of HER2/EGFR 1+1+2 Hi, a heterodimeric 1+1+2Hi format antibody that can bind both HER2 and EGFR, either simultaneously or separately. Design of the 1+1+2 Hi format antibody is shown on the right side. Homodimeric formats against HER2 and EGFR were included for reference. For this binding assay, Desmoplastic Small Cell Round Tumor cells (JN-DSRCT1) were incubated with each antibody for 30 minutes at 4° C., washed and incubated with a fluorescent anti-human secondary antibody. After the final wash, the cells were analyzed using flow cytometry. In this example, the binding of the high affinity 1+1+2 HDTVS antibody was stronger than that of either anti-HER2 or anti-EGFR homodimeric antibodies, while maintaining specificity for both antigens, demonstrating cooperative binding.

[0054] FIG. **15** demonstrates the combined binding effect of GD2/B7H3 1+1+2 Lo, a heterodimeric 1+1+2Lo format antibody that can bind both GD2 and B7H3 simultaneously. Design of the 1+1+2 Lo format antibody is shown on the left hand side. Homodimeric formats against GD2 and B7H3, and monovalent control antibodies against GD2 or B7H3 (GD2 or B7H3 ctrl, respectively) were included for reference. For this binding assay, Osteosarcoma cells (U2OS) were incubated with each antibody for 30 minutes at 4° C., washed and incubated with a fluorescent anti-human secondary antibody. After the final wash, the cells were analyzed using flow cytometry. In this example, the binding of

the low affinity 1+1+2 HDTVS antibody was similar to the anti-B7H3 homodimeric antibody, but weaker than the anti-GD2 homodimeric antibody. Importantly, GD2/B7H3 1+1+2 Lo also showed improved binding over monovalent control antibodies, demonstrating cooperative binding.

[0055] FIG. **16** demonstrates the cytotoxic selectivity of HER2/GD2 1+1+2 Lo, a heterodimeric 1+1+2Lo format that can bind both GD2 and HER2 simultaneously. In this format, a low affinity HER2 sequence was used. Design of the 1+1+2 Lo format antibody is shown below the line graph. Homodimeric formats against GD2 and HER2, and monovalent control antibodies against GD2 or HER2 (GD2 and HER2 ctrl, respectively) were included for reference. For this cytotoxicity assay, Osteosarcoma cells (U2OS) were first incubated with ^{51}Cr for one hour. After the incubation, the ^{51}Cr labeled target cells were mixed with serial dilutions of the indicated antibody and activated human T-cells for four hours at 37° C. After four hours, supernatant was harvested and analyzed on a gamma counter to quantify the released ^{51}Cr. Cytotoxicity was measured as the % of released ^{51}Cr from maximum release. In this example, the low affinity 1+1+2 heterodimer antibody killed the target cells as effectively as the anti-GD2 and anti-HER2 homodimeric antibodies yet showing clear superiority over the monovalent control formats. This demonstrates the selectivity possible with the 1+1+2Lo design: target cells expressing each individual antigen will be targeted with 10-100-fold lower cytotoxic potency than targets expressing both antigens simultaneously. Using a homodimeric design for either GD2 or HER2 would lose such selectivity.

[0056] FIG. **17***a* demonstrates the cytotoxic dual specificity of HER2/GPA33 1+1+2 Hi, a heterodimeric 1+1+2Hi format that can bind both GPA33 and HER2 simultaneously. Design of the 1+1+2 Hi format antibody is shown below the line graph. Homodimeric formats against GPA33 and HER2, and monovalent control antibodies against GPA33 or HER2 were included for reference. For this cytotoxicity assay, Colon cancer cells (Colo205) were first incubated with ^{51}Cr for one hour. After the incubation, the ^{51}Cr labeled target cells were mixed with serial dilutions of the indicated antibody and activated human T-cells for four hours at 37° C. After four hours, the supernatant was harvested and read on a gamma counter to quantify the released ^{51}Cr. Cytotoxicity was measured as the % of released ^{51}Cr from maximum release. In this example, the high affinity 1+1+2 heterodimer antibody killed target cells as effectively as the anti-GPA33 homodimeric antibody, but with greater potency than the anti-HER2 homodimeric antibody and monovalent control antibodies. These data demonstrate functional cooperativity between the HER2 and GPA33 antigen-binding domains and illustrate that the dual specificity of a 1+1+2Hi format does not significantly compromise its cytotoxicity against either antigen individually.

[0057] FIG. **17***b* demonstrates the combined binding effect of HER2/GPA33 1+1+2 Hi, a heterodimeric 1+1+2Hi format that can bind both HER2 and GPA33, either simultaneously or separately. Design of the 1+1+2 Hi format antibody is shown on the right hand side. For this binding assay, Colon cancer cells (Colo205) were incubated with each antibody for 30 minutes at 4° C., washed and incubated with a fluorescent anti-human secondary antibody. After the final wash, the cells were analyzed using flow cytometry. In this example, the affinity binding of the 1+1+2 heterodimer antibody was stronger than either anti-HER2 or anti-GPA33 homodimeric and monovalent control antibodies, while maintaining specificity for both antigens, demonstrating cooperative binding.

[0058] FIG. **18** demonstrates the utility of CD3/CD28 2+1+1, a heterodimeric 2+1+1 design that can bind both CD3 and CD28 on T-cells. Design of the heterodimeric 1+1+2 format antibody is shown below the line graph. Homodimeric formats against CD3 and CD28 were included for reference. For this cytokine assay, naïve human T-cells and Melanoma tumor cells (M14) were co-cultured along with the indicated BsAb for 20 hours before culture supernatants were harvested and analyzed for secreted cytokine IL-2 by flow cytometry. Data was normalized to T-cell cytokine release after 20 hours without target cells or antibody. The CD3/CD28 2+1+1 design showed clearly more potent cytokine release activity than either CD3 or CD28 engagement alone, illustrating cooperative activity from dual CD3/CD28 engagement.

[0059] FIG. **19** demonstrates the combined binding effect of CD3/CD4 2+1+1, a heterodimeric 2+1+1 format antibody that can bind both CD3 and CD4 simultaneously. Design of the heterodimeric 2+1+1 format antibody is shown on the right side. For this binding assay, active human T cells were incubated with each antibody for 30 minutes at 4° C., washed and incubated with a fluorescent anti-human secondary antibody. After the final wash, the cells were analyzed using flow cytometry. In this example, the 2+1+1 heterodimer shows enhanced binding compared to the bivalent CD4 and monomeric CD3 binder (2+1) demonstrating cooperative binding.

[0060] FIG. **20** demonstrates the combined binding effect of CD3/PD-1 2+1+1, a heterodimeric 2+1+1 format antibody that can bind both CD3 and PD-1 simultaneously. Design of the heterodimeric 2+1+1 format antibody is shown on the right side. For this binding assay active human T cells were incubated with each antibody for 30 minutes at 4° C., washed and incubated with a fluorescent anti-human secondary antibody. After the final wash, the cells were analyzed using flow cytometry. In this example, the binding of the 2+1+1 heterodimer was better than either anti-PD-1 homodimeric or anti-CD3 monomeric (2+1) binder, demonstrating cooperative binding.

[0061] FIGS. **21***a*-**21***c* show the unique characteristics of the IgG-L-scFv design, compared to two other common dual bivalent design strategies: the BiTE-Fc and the IgG-H-scFv. FIG. **21***a* demonstrates the potent T-cell functional activity of the IgG-L-scFv design compared to other dual bivalent T-cell bispecific antibody formats. Designs of the IgG-L-scFv, BiTE-Fc and the IgG-H-scFv format antibodies are shown below the line graph. For this cytokine assay, naïve T-cells and melanoma tumor cells (M14) were co-cultured along with each BsAb for 20 hours before culture supernatants were harvested and analyzed for secreted cytokine IL-2 by flow cytometry. Data were normalized to T-cell cytokine release after 20 hours without target cells or antibody. In contrast to the IgG-H-scFv (2+2HC) and the BiTE-Fc (2+2B) designs, the IgG-L-scFv format (2+2) demonstrated significant cytokine IL-2 responses in vitro, which correlated with stronger in vivo activity (shown in FIG. **21***c*). FIG. **21***b* illustrates the unusually weak T-cell binding activity of the IgG-L-scFv design compared to other dual bivalent T-cell bispecific antibody formats. For this binding assay, T-cells and melanoma tumor cells (M14) were separately incubated with each antibody for 30 minutes at 4° C.,

washed and incubated with a fluorescent anti-human secondary antibody. After the final wash, the cells were analyzed using flow cytometry. Shown is CD3-specific (FIG. **21***b*, upper panel), and GD2-specific binding (FIG. **21***b*, middle panel). Designs of the IgG-L-scFv, BiTE-Fc and the IgG-H-scFv format antibodies are shown in FIG. **21***b* (lower panel). In contrast to their GD2 binding activity, each BsAb demonstrated quite different T-cell binding activities. These data demonstrated how the IgG-L-scFv design is uniquely different than other dual-bivalent designs, with each scFv showing incomplete bivalent binding. Although the inclusion of two scFv domains in the IgG-L-scFv does show improvement over monovalent designs, it still does not compare to the binding activity of the 2+2HC or 2+2B designs, illustrating the sterically hindered binding of this format. FIG. **21***c* illustrates the in vivo superiority of the IgG-L-scFv design. In contrast to other dual bivalent designs, the IgG-L-scFv format was the only one capable of controlling tumor growth in mice. Here, immunodeficient mice (Balb/c IL-2Rgc−/−, Rag2−/−) were implanted with neuroblastoma cells (IMR32) subcutaneously, before being treated with intravenous activated T-cells and antibody (2-times per week). Tumors sizes were measured by caliper.

[0062] FIG. **22** demonstrates the in vitro properties and design of anti-CD33/CD3 IgG-[L]-scFv panel. The in vitro cytotoxicity EC_{50}, fold-difference in EC_{50}, antigen valency, heterodimer design and protein purity by SEC-HPLC for anti-CD33/CD3 IgG-[L]-scFv panel are summarized. Fold change is based on the EC_{50} of 2+2. Purity was calculated as the fraction of protein at correct elution time out of the total protein by area under the curve of the SEC-HPLC chromatogram. For the cytotoxicity assays, CD33-transfected cells (Nalm6) were first incubated with ^{51}Cr for one hour. Afterwards, ^{51}Cr labeled target cells were mixed with serial titrations of the indicated antibody and activated human T-cells for four hours at 37° C. The supernatant was harvested and analyzed on a gamma counter to quantify the released ^{51}Cr. Cytotoxicity was measured as the % of released ^{51}Cr from maximum release. These results confirm the relative importance of Cis-oriented binding domains in an additional antigen system (CD33) which is much more membrane distal than GD2 (see FIG. **5**).

[0063] FIG. **23** provides a summary of the various HDTVS antibodies tested in the Examples disclosed herein. The table summarizes all successfully produced HDTVS formatted multi-specific antibodies across a variety of antigen models. All clones were expressed in Expi293 cells and heterodimerized using the controlled Fab Arm Exchange method. HDTVS type displays the category of each clone. Fab 1 and scFv 1 (and corresponding Ag1 and Ag3) are attached in a cis-orientation on one heavy chain (linked by the light chain of Fab) while Fab 2 and scFv 2 (and corresponding Ag2 and Ag4) are on a separate heavy chain molecule in a cis-orientation (linked by the light chain of Fab).

DETAILED DESCRIPTION

[0064] It is to be appreciated that certain aspects, modes, embodiments, variations and features of the present methods are described below in various levels of detail in order to provide a substantial understanding of the present technology.

[0065] In practicing the present methods, many conventional techniques in molecular biology, protein biochemistry, cell biology, immunology, microbiology and recombinant DNA are used. See, e.g., Sambrook and Russell eds. (2001) *Molecular Cloning: A Laboratory Manual,* 3rd edition; the series Ausubel et al. eds. (2007) *Current Protocols in Molecular Biology*; the series *Methods in Enzymology* (Academic Press, Inc., N.Y.); MacPherson et al. (1991) PCR 1*: A Practical Approach* (IRL Press at Oxford University Press); MacPherson et al. (1995) PCR 2*: A Practical Approach*; Harlow and Lane eds. (1999) *Antibodies, A Laboratory Manual*; Freshney (2005) *Culture of Animal Cells: A Manual of Basic Technique,* 5th edition; Gait ed. (1984) *Oligonucleotide Synthesis*; U.S. Pat. No. 4,683,195; Hames and Higgins eds. (1984) *Nucleic Acid Hybridization*; Anderson (1999) *Nucleic Acid Hybridization*; Hames and Higgins eds. (1984) *Transcription and Translation; Immobilized Cells and Enzymes* (IRL Press (1986)); Perbal (1984) *A Practical Guide to Molecular Cloning*; Miller and Calos eds. (1987) *Gene Transfer Vectors for Mammalian Cells* (Cold Spring Harbor Laboratory); Makrides ed. (2003) *Gene Transfer and Expression in Mammalian Cells*; Mayer and Walker eds. (1987) *Immunochemical Methods in Cell and Molecular Biology* (Academic Press, London); and Herzenberg et al. eds (1996) *Weir's Handbook of Experimental Immunology*. Methods to detect and measure levels of polypeptide gene expression products (i.e., gene translation level) are well-known in the art and include the use of polypeptide detection methods such as antibody detection and quantification techniques. (See also, Strachan & Read, *Human Molecular Genetics*, Second Edition. (John Wiley and Sons, Inc., NY, 1999)).

[0066] Advances in protein engineering can enhance the functional output of proteins by linking different peptides in sequences, or by arranging them in complexes that do not exist naturally. Antibodies have served as a platform for such enhancements, where antigen binding can be modulated through antigen affinity maturation (Boder et al., *Proc Natl Acad Sci* USA 97:10701-10705 (2000)) or increases in valency (Cuesta et al., *Trends Biotechnol* 28:355-362 (2010)). Fc receptor binding can be modulated through point mutations (Leabman et al., *MAbs* 5:896-903 (2013)) or changes in glycosylation (Xu et al., *Cancer Immun Res* 4: 631-638 (2016)) whereas pharmacokinetics can be influenced through ablation of FcR(n) binding (Suzuki et al., *J Immunol* 184:1968-1976 (2010)) or removal of entire antibody domains. However, no single antibody platform to date has shown a clear and significant functional advantage over others within the clinic.

[0067] The present disclosure provides an antibody platform in which up to 4 different antigen binding domains can be used to simultaneously engage up to 4 different cellular targets, thereby increasing avidity and modulating specificity of the therapeutic antibodies. This platform is based on the heterodimerization of two IgG half molecules, in which each IgG half molecule comprises a heavy chain and a light chain, wherein a scFv is linked to the C-terminus of at least one light chain (i.e., IgG-[L]-scFv platform). The resulting heterodimers are both trivalent/tetravalent and multispecific and are collectively referred to as HDTVS antibodies.

[0068] The native form of the IgG-[L]-scFv platform has bivalent binding to two different targets (2+2) (each integer represents a different specificity, while its value represents the valency). The present disclosure provides 5 HDTVS platform variants which vary the 4 functional domains (2 Fabs and 2 scFv) in the IgG(L)-scFv format: (1) the Lo1+

1+2 HDTVS variant to achieve improved tumor cell specificity, (2) the Hi1+1+2 HDTVS variant to achieve broader tumor cell selectivity, (3) the 2+1+1 HDTVS variant to achieve improved immune cell activation, (4) the 2+1+1 HDTVS variant which allows recruitment of different cells and/or payloads and (5) the 1+1+1+1 HDTVS variant which combines designs from (1) or (2) with (3) or (4) to achieve more effective immune activation or payload delivery with finer specificity or broader selectivity. (FIGS. **1***a*-**1***f*). In order to test the functional output of these HDTVS variants, one of the 2 Fab domains can be neutralized by using an irrelevant Fab that has no binding to either tumor cells or effector immune cells (e.g., T cells), creating monovalency for tumor. Alternatively, one of the scFv domains can be removed to create monovalency towards effector immune cells (e.g., T cells).

[0069] As described herein, the biological potency of each design is dependent on the biophysical characteristics of the antigen binding domains of the HDTVS variants. Unexpectedly, the changes in valency did not entirely correlate with changes in functional output. As shown in Examples described herein, the biological activity of the tri- and tetra-specific variants of the HDTVS platform is dependent on the antigen/epitope combinations, as well as the relative binding affinities to each target antigen (up to 4 targets total). The Lo1+1+2 HDTVS variant requires its Fab domains to bind to two distinct tumor antigens that are within a proximity of 60-120 angstroms from each other (thus allowing simultaneous binding), and (b) have monovalent and/or effective binding affinities (K_D) that range from about 100 nM to about 100 pM to reduce bystander reactivity with healthy cells. The Hi1+1+2 HDTVS variant on the other hand exploits the high monovalent and/or effective binding affinity (K_D<100 pM) of its Fab domains such that monovalency is nearly as effective as bivalency. Moreover, the 2+1+1 HDTVS variant exhibited in vivo tumor clearance activity that was comparable to that observed with the 2+2 native form of the IgG-[L]-scFv platform. These results were unexpected given that the binding activities of the 2+1+1 HDTVS variant were about 6-fold lower than the 2+2 native form of the IgG-[L]-scFv platform.

[0070] Accordingly, biophysical properties such as orientation (cis vs trans), valency (mono- vs bi-valent) and target affinity (K_D~nM or <pM) had an unpredictable impact on the functionality of the HDTVS variants (e.g., log-fold enhancement of therapeutic efficacy). Moreover, the HDTVS antibodies of the present technology show superior therapeutic potency compared to other conventional antibody platforms, such as BiTE or heterodimeric IgG (IgG-Het). These results also demonstrate that different multispecific antibody platforms yield antibodies that possess substantially different biological properties. Without wishing to be bound by theory, it is believed that spatial distances between the antigen binding domains of multispecific antibodies, as well as the relative flexibility and orientation of the individual antigen binding domains may determine their ability to drive cell-to-cell interactions.

Definitions

[0071] Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this technology belongs. As used in this specification and the appended claims, the singular forms "a", "an" and "the" include plural referents unless the content clearly dictates otherwise. For example, reference to "a cell" includes a combination of two or more cells, and the like. Generally, the nomenclature used herein and the laboratory procedures in cell culture, molecular genetics, organic chemistry, analytical chemistry and nucleic acid chemistry and hybridization described below are those well-known and commonly employed in the art.

[0072] As used herein, a "2+1+1" design refers to a HDTVS antibody in which the two Fab domains recognize and bind to the same target antigen, and the two scFvs recognize and bind to two distinct target antigens. In some embodiments, the two scFvs of the 2+1+1 HDTVS antibody binds to two distinct target antigens that are up to 180 angstroms apart from each other in order to engage two separate molecules on the same cell.

[0073] As used herein, the term "about" in reference to a number is generally taken to include numbers that fall within a range of 1%, 5%, or 10% in either direction (greater than or less than) of the number unless otherwise stated or otherwise evident from the context (except where such number would be less than 0% or exceed 100% of a possible value).

[0074] As used herein, the "administration" of an agent or drug to a subject includes any route of introducing or delivering to a subject a compound to perform its intended function. Administration can be carried out by any suitable route, including but not limited to, orally, intranasally, parenterally (intravenously, intramuscularly, intraperitoneally, or subcutaneously), rectally, intrathecally, intratumorally or topically. Administration includes self-administration and the administration by another.

[0075] As used herein, the term "antibody" collectively refers to immunoglobulins or immunoglobulin-like molecules including by way of example and without limitation, IgA, IgD, IgE, IgG and IgM, combinations thereof, and similar molecules produced during an immune response in any vertebrate, for example, in mammals such as humans, goats, rabbits and mice, as well as non-mammalian species, such as shark immunoglobulins. As used herein, "antibodies" (includes intact immunoglobulins) and "antigen binding fragments" specifically bind to a molecule of interest (or a group of highly similar molecules of interest) to the substantial exclusion of binding to other molecules (for example, antibodies and antibody fragments that have a binding constant for the molecule of interest that is at least 10^3 greater, at least $10^4 M^{-1}$ greater or at least 10^5 greater than a binding constant for other molecules in a biological sample). The term "antibody" also includes genetically engineered forms such as chimeric antibodies (for example, humanized murine antibodies), heteroconjugate antibodies (such as, bispecific antibodies). See also, Pierce Catalog and Handbook, 1994-1995 (Pierce Chemical Co., Rockford, Ill.); Kuby, J., *Immunology,* 3rd Ed., W.H. Freeman & Co., New York, 1997.

[0076] More particularly, antibody refers to a polypeptide ligand comprising at least a light chain immunoglobulin variable region or heavy chain immunoglobulin variable region which specifically recognizes and binds an epitope of an antigen. Antibodies are composed of a heavy and a light chain, each of which has a variable region, termed the variable heavy (V_H) region and the variable light (V_L) region. Together, the VH region and the VL region are responsible for binding the antigen recognized by the anti-

body. Typically, an immunoglobulin has heavy (H) chains and light (L) chains interconnected by disulfide bonds. There are two types of light chain, lambda (λ) and kappa (κ). There are five main heavy chain classes (or isotypes) which determine the functional activity of an antibody molecule: IgM, IgD, IgG, IgA and IgE. Each heavy and light chain contains a constant region and a variable region, (the regions are also known as "domains"). In combination, the heavy and the light chain variable regions specifically bind the antigen. Light and heavy chain variable regions contain a "framework" region interrupted by three hypervariable regions, also called "complementarity-determining regions" or "CDRs". The extent of the framework region and CDRs have been defined (see, Kabat et al., *Sequences of Proteins of Immunological Interest*, U.S. Department of Health and Human Services, 1991, which is hereby incorporated by reference). The Kabat database is now maintained online. The sequences of the framework regions of different light or heavy chains are relatively conserved within a species. The framework region of an antibody, that is the combined framework regions of the constituent light and heavy chains, largely adopt a β-sheet conformation and the CDRs form loops which connect, and in some cases form part of, the β-sheet structure. Thus, framework regions act to form a scaffold that provides for positioning the CDRs in correct orientation by inter-chain, non-covalent interactions.

[0077] The CDRs are primarily responsible for binding to an epitope of an antigen. The CDRs of each chain are typically referred to as CDR1, CDR2, and CDR3, numbered sequentially starting from the N-terminus, and are also typically identified by the chain in which the particular CDR is located. Thus, a V_H CDR3 is located in the variable domain of the heavy chain of the antibody in which it is found, whereas a V_L CDR1 is the CDR1 from the variable domain of the light chain of the antibody in which it is found. An antibody that binds a target antigen will have a specific V_H region and the V_L region sequence, and thus specific CDR sequences. Antibodies with different specificities (i.e. different combining sites for different antigens) have different CDRs. Although it is the CDRs that vary from antibody to antibody, only a limited number of amino acid positions within the CDRs are directly involved in antigen binding. These positions within the CDRs are called specificity determining residues (SDRs). "Immunoglobulin-related compositions" as used herein, refers to antibodies (including monoclonal antibodies, polyclonal antibodies, humanized antibodies, chimeric antibodies, recombinant antibodies, multispecific antibodies, bispecific antibodies, etc.,) as well as antibody fragments. An antibody or antigen binding fragment thereof specifically binds to an antigen.

[0078] As used herein, the term "antibody-related polypeptide" means antigen binding antibody fragments, including single-chain antibodies, that can comprise the variable region(s) alone, or in combination, with all or part of the following polypeptide elements: hinge region, CH_1, CH_2, and CH_3 domains of an antibody molecule. Also included in the technology are any combinations of variable region(s) and hinge region, CH_1, CH_2, and CH_3 domains. Antibody-related molecules useful in the present methods, e.g., but are not limited to, Fab, Fab' and $F(ab')_2$, Fd, single-chain Fvs (scFv), single-chain antibodies, disulfide-linked Fvs (sdFv) and fragments comprising either a V_L or V_H domain. Examples include: (i) a Fab fragment, a monovalent fragment consisting of the V_L, V_H, C_L and CH_1 domains; (ii) a $F(ab')_2$ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the V_H and CH_1 domains; (iv) a Fv fragment consisting of the V_L and V_H domains of a single arm of an antibody, (v) a dAb fragment (Ward et al., *Nature* 341: 544-546, 1989), which consists of a V_H domain; and (vi) an isolated complementarity determining region (CDR). As such "antibody fragments" or "antigen binding fragments" can comprise a portion of a full-length antibody, generally the antigen binding or variable region thereof. Examples of antibody fragments or antigen binding fragments include Fab, Fab', $F(ab')_2$, and Fv fragments; diabodies; linear antibodies; single-chain antibody molecules; and multispecific antibodies formed from antibody fragments.

[0079] "Bispecific antibody" or "BsAb", as used herein, refers to an antibody that can bind simultaneously to two targets that have a distinct structure, e.g., two different target antigens, two different epitopes on the same target antigen, or a hapten and a target antigen or epitope on a target antigen. A variety of different bispecific antibody structures are known in the art. In some embodiments, each antigen binding moiety in a bispecific antibody includes V_H and/or V_L regions; in some such embodiments, the V_H and/or V_L regions are those found in a particular monoclonal antibody. In some embodiments, the bispecific antibody contains two antigen binding moieties, each including VH and/or VL regions from different monoclonal antibodies. In some embodiments, the bispecific antibody contains two antigen binding moieties, wherein one of the two antigen binding moieties includes an immunoglobulin molecule having VH and/or VL regions that contain CDRs from a first monoclonal antibody, and the other antigen binding moiety includes an antibody fragment (e.g., Fab, F(ab'), $F(ab')_2$, Fd, Fv, dAB, scFv, etc.) having VH and/or VL regions that contain CDRs from a second monoclonal antibody.

[0080] As used herein, the term "diabodies" refers to small antibody fragments with two antigen binding sites, which fragments comprise a heavy-chain variable domain (VH) connected to a light-chain variable domain (VL) in the same polypeptide chain (VH VL). By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen binding sites. Diabodies are described more fully in, e.g., EP 404,097; WO 93/11161; and 30 Hollinger et al., Proc. Natl. Acad. Sci. USA, 90: 6444-6448 (1993).

[0081] As used herein, the terms "single-chain antibodies" or "single-chain Fv (scFv)" refer to an antibody fusion molecule of the two domains of the Fv fragment, VL and VH. Single-chain antibody molecules may comprise a polymer with a number of individual molecules, for example, dimer, trimer or other polymers. Furthermore, although the two domains of the F_v fragment, V_L and V_H, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the V_L and V_H regions pair to form monovalent molecules (known as single-chain F_v (scFv)). Bird et al. (1988) *Science* 242:423-426 and Huston et al. (1988) *Proc. Natl. Acad Sci.* USA 85:5879-5883. Such single-chain antibodies can be prepared by recombinant techniques or enzymatic or chemical cleavage of intact antibodies.

[0082] Any of the above-noted antibody fragments are obtained using conventional techniques known to those of

skill in the art, and the fragments are screened for binding specificity and neutralization activity in the same manner as are intact antibodies.

[0083] As used herein, an "antigen" refers to a molecule to which an antibody (or antigen binding fragment thereof) can selectively bind. The target antigen may be a protein, carbohydrate, nucleic acid, lipid, hapten, or other naturally occurring or synthetic compound. In some embodiments, the target antigen may be a polypeptide. An antigen may also be administered to an animal to generate an immune response in the animal.

[0084] The term "antigen binding fragment" refers to a fragment of the whole immunoglobulin structure which possesses a part of a polypeptide responsible for binding to antigen. Examples of the antigen binding fragment useful in the present technology include scFv, $(scFv)_2$, scFvFc, Fab, Fab' and $F(ab')_2$, but are not limited thereto.

[0085] By "binding affinity" is meant the strength of the total noncovalent interactions between a single binding site of a molecule (e.g., an antibody) and its binding partner (e.g., an antigen). The affinity of a molecule X for its partner Y can generally be represented by the dissociation constant (Ku). Affinity can be measured by standard methods known in the art, including those described herein. A low-affinity complex contains an antibody that generally tends to dissociate readily from the antigen, whereas a high-affinity complex contains an antibody that generally tends to remain bound to the antigen for a longer duration.

[0086] As used herein, the term "biological sample" means sample material derived from living cells. Biological samples may include tissues, cells, protein or membrane extracts of cells, and biological fluids (e.g., ascites fluid or cerebrospinal fluid (CSF)) isolated from a subject, as well as tissues, cells and fluids present within a subject. Biological samples of the present technology include, but are not limited to, samples taken from breast tissue, renal tissue, the uterine cervix, the endometrium, the head or neck, the gallbladder, parotid tissue, the prostate, the brain, the pituitary gland, kidney tissue, muscle, the esophagus, the stomach, the small intestine, the colon, the liver, the spleen, the pancreas, thyroid tissue, heart tissue, lung tissue, the bladder, adipose tissue, lymph node tissue, the uterus, ovarian tissue, adrenal tissue, testis tissue, the tonsils, thymus, blood, hair, buccal, skin, serum, plasma, CSF, semen, prostate fluid, seminal fluid, urine, feces, sweat, saliva, sputum, mucus, bone marrow, lymph, and tears. Biological samples can also be obtained from biopsies of internal organs or from cancers. Biological samples can be obtained from subjects for diagnosis or research or can be obtained from non-diseased individuals, as controls or for basic research. Samples may be obtained by standard methods including, e.g., venous puncture and surgical biopsy. In certain embodiments, the biological sample is a breast, lung, colon, or prostate tissue sample obtained by needle biopsy.

[0087] As used herein, the term "cancer" refers to a neoplasm or tumor resulting from abnormal uncontrolled growth of cells. In some embodiments, cancer refers to a benign tumor or a malignant tumor. In some embodiments, the cancer is associated with a specific cancer antigen.

[0088] As used herein, the term "CDR-grafted antibody" means an antibody in which at least one CDR of an "acceptor" antibody is replaced by a CDR "graft" from a "donor" antibody possessing a desirable antigen specificity.

[0089] As used herein, the term "chimeric antibody" means an antibody in which the Fc constant region of a monoclonal antibody from one species (e.g., a mouse Fc constant region) is replaced, using recombinant DNA techniques, with an Fc constant region from an antibody of another species (e.g., a human Fc constant region). See generally, Robinson et al., PCT/US86/02269; Akira et al., European Patent Application 184,187; Taniguchi, European Patent Application 171,496; Morrison et al., European Patent Application 173,494; Neuberger et al., WO 86/01533; Cabilly et al. U.S. Pat. No. 4,816,567; Cabilly et al., European Patent Application 0125,023; Better et al., *Science* 240: 1041-1043, 1988; Liu et al., *Proc. Natl. Acad. Sci.* USA 84: 3439-3443, 1987; Liu et al., *J. Immunol* 139: 3521-3526, 1987; Sun et al., *Proc. Natl. Acad. Sci.* USA 84: 214-218, 1987; Nishimura et al., *Cancer Res* 47: 999-1005, 1987; Wood et al., Nature 314: 446-449, 1885; and Shaw et al., *J. Natl. Cancer Inst.* 80: 1553-1559, 1988.

[0090] As used herein, the term "consensus FR" means a framework (FR) antibody region in a consensus immunoglobulin sequence. The FR regions of an antibody do not contact the antigen.

[0091] As used herein, a "control" is an alternative sample used in an experiment for comparison purpose. A control can be "positive" or "negative." For example, where the purpose of the experiment is to determine a correlation of the efficacy of a therapeutic agent for the treatment for a particular type of disease, a positive control (a compound or composition known to exhibit the desired therapeutic effect) and a negative control (a subject or a sample that does not receive the therapy or receives a placebo) are typically employed.

[0092] As used herein, the term "effective affinity" refers to the binding constant derived from measuring the overall binding kinetics of a compound with two or more simultaneous binding interactions (e.g., with an IgG, IgM, IgA, IgD, or IgE molecule instead of a Fab domain).

[0093] As used herein, the term "effective amount" refers to a quantity sufficient to achieve a desired therapeutic and/or prophylactic effect, e.g., an amount which results in the prevention of, or a decrease in a disease or condition described herein or one or more signs or symptoms associated with a disease or condition described herein. In the context of therapeutic or prophylactic applications, the amount of a composition administered to the subject will vary depending on the composition, the degree, type, and severity of the disease and on the characteristics of the individual, such as general health, age, sex, body weight and tolerance to drugs. The skilled artisan will be able to determine appropriate dosages depending on these and other factors. The compositions can also be administered in combination with one or more additional therapeutic compounds. In the methods described herein, the therapeutic compositions may be administered to a subject having one or more signs or symptoms of a disease or condition described herein. As used herein, a "therapeutically effective amount" of a composition refers to composition levels in which the physiological effects of a disease or condition are ameliorated or eliminated. A therapeutically effective amount can be given in one or more administrations.

[0094] As used herein, the term "effector cell" means an immune cell which is involved in the effector phase of an immune response, as opposed to the cognitive and activation phases of an immune response. Exemplary immune cells include a cell of a myeloid or lymphoid origin, e.g., lym-

phocytes (e.g., B cells and T cells including cytolytic T cells (CTLs)), killer cells, natural killer cells, macrophages, monocytes, eosinophils, neutrophils, polymorphonuclear cells, granulocytes, mast cells, and basophils. Effector cells express specific Fc receptors and carry out specific immune functions. An effector cell can induce antibody-dependent cell-mediated cytotoxicity (ADCC), e.g., a neutrophil capable of inducing ADCC. For example, monocytes, macrophages, neutrophils, eosinophils, and lymphocytes which express FcaR are involved in specific killing of target cells and presenting antigens to other components of the immune system, or binding to cells that present antigens.

[0095] "Effector function" as used herein refers to a biochemical event that results from the interaction of an antibody Fc region with an Fc receptor or an antigen. Effector functions include but are not limited to antibody dependent cell mediated cytotoxicity (ADCC), antibody dependent cell mediated phagocytosis (ADCP), and complement dependent cytotoxicity (CDC). Effector functions include both those that operate after the binding of an antigen and those that operate independent of antigen binding.

[0096] As used herein, the term "epitope" means an antigenic determinant (site on an antigen) capable of specific binding to an antibody. Epitopes usually comprise chemically active surface groupings of molecules such as amino acids or sugar side chains and may have specific three-dimensional structural characteristics, as well as specific charge characteristics. Conformational and non-conformational epitopes are distinguished in that the binding to the former but not the latter is lost in the presence of denaturing solvents. Thus, in some embodiments, the heterodimeric trivalent/tetravalent multispecific antibodies disclosed herein may bind a non-conformational epitope and/or a conformational epitope. To screen for antibodies which bind to an epitope, a routine cross-blocking assay such as that described in Antibodies, *A Laboratory Manual*, Cold Spring Harbor Laboratory, Ed Harlow and David Lane (1988), can be performed. This assay can be used to determine if an antibody binds the same site or epitope as a heterodimeric trivalent/tetravalent multispecific antibody of the present technology. Alternatively, or additionally, epitope mapping can be performed by methods known in the art. For example, the antibody sequence can be mutagenized such as by alanine scanning, to identify contact residues. In a different method, peptides corresponding to different regions of a target protein antigen can be used in competition assays with the test antibodies or with a test antibody and an antibody with a characterized or known epitope.

[0097] As used herein, "expression" includes one or more of the following: transcription of the gene into precursor mRNA; splicing and other processing of the precursor mRNA to produce mature mRNA; mRNA stability; translation of the mature mRNA into protein (including codon usage and tRNA availability); and glycosylation and/or other modifications of the translation product, if required for proper expression and function.

[0098] As used herein, the term "gene" means a segment of DNA that contains all the information for the regulated biosynthesis of an RNA product, including promoters, exons, introns, and other untranslated regions that control expression.

[0099] As used herein, a "heterodimerization domain that is incapable of forming a stable homodimer" refers to a member of a pair of distinct but complementary chemical motifs (e.g., amino acids, nucleotides, sugars, lipids, synthetic chemical structures, or any combination thereof) which either exclusively self-assembles as a heterodimer with the second complementary member of the pair, or shows at least a 10^4 fold preference for assembling into a heterodimer with the second complementary member of the pair, or forms a homodimer with an identical member that is not stable under reducing conditions such as >2 mM 2-MEA at room temperature for 90 minutes (see e.g., Labrijn, A. F. et al., *Proc. Natl. Acad. Sci.* 110, 5145-50 (2013). Examples of such heterodimerization domains include, but are not limited to CH2-CH3 that include any of the Fc variants/mutations described herein, WinZip-A1B1, a pair of complementary oligonucleotides, and a CH-1 and CL pair.

[0100] As used herein, "Hi1+1+2" refers to a heterodimeric tetravalent multispecific antibody in which the Fab domains (a) bind to two distinct target epitopes and (b) have monovalent binding affinities or effective affinities (K_D) that are <100 pM.

[0101] As used herein, the term "humanized" forms of non-human (e.g., murine) antibodies are chimeric antibodies which contain minimal sequence derived from non-human immunoglobulin. For the most part, humanized antibodies are human immunoglobulins in which hypervariable region residues of the recipient are replaced by hypervariable region residues from a non-human species (donor antibody) such as mouse, rat, rabbit or nonhuman primate having the desired specificity, affinity, and capacity. In some embodiments, Fv framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, humanized antibodies may comprise residues which are not found in the recipient antibody or in the donor antibody. These modifications are made to further refine antibody performance such as binding affinity. Generally, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains (e.g., Fab, Fab', $F(ab')_2$, or Fv), in which all or substantially all of the hypervariable loops correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin consensus FR sequence although the FR regions may include one or more amino acid substitutions that improve binding affinity. The number of these amino acid substitutions in the FR is typically no more than 6 in the H chain, and in the L chain, no more than 3. The humanized antibody optionally may also comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. For further details, see Jones et al., *Nature* 321: 522-525 (1986); Reichmann et al., *Nature* 332:323-329 (1988); and Presta, *Curr. Op. Struct. Biol.* 2:593-596 (1992). See e.g., Ahmed & Cheung, *FEBS Letters* 588(2):288-297 (2014).

[0102] As used herein, the term "hypervariable region" refers to the amino acid residues of an antibody which are responsible for antigen binding. The hypervariable region generally comprises amino acid residues from a "complementarity determining region" or "CDR" (e.g., around about residues 24-34 (L1), 50-56 (L2) and 89-97 (L3) in the V_L, and around about 31-35B (H1), 50-65 (H2) and 95-102 (H3) in the V_H (Kabat et al., *Sequences of Proteins of Immunological Interest,* 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1991)) and/or those residues from a "hypervariable loop" (e.g., residues 26-32 (L1), 50-52 (L2) and 91-96 (L3) in the V_L, and 26-32 (H1),

52A-55 (H2) and 96-101 (H3) in the V_H (Chothia and Lesk *J. Mol. Biol.* 196:901-917 (1987)).

[0103] As used herein, the term "intact antibody" or "intact immunoglobulin" means an antibody that has at least two heavy (H) chain polypeptides and two light (L) chain polypeptides interconnected by disulfide bonds. Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as HCVR or V_H) and a heavy chain constant region. The heavy chain constant region is comprised of three domains, CH_1, CH_2 and CH_3. Each light chain is comprised of a light chain variable region (abbreviated herein as LCVR or V_L) and a light chain constant region. The light chain constant region is comprised of one domain, CL. The V_H and V_L regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each V_H and V_L is composed of three CDRs and four FRs, arranged from amino-terminus to carboxyl-terminus in the following order: FR_1, CDR_1, FR_2, CDR_2, FR_3, CDR_3, FR_4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The constant regions of the antibodies can mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (e.g., effector cells) and the first component (Clq) of the classical complement system.

[0104] As used herein, the terms "individual", "patient", or "subject" can be an individual organism, a vertebrate, a mammal, or a human. In some embodiments, the individual, patient or subject is a human.

[0105] As used herein, "Lo1+1+2" refers to a heterodimeric tetravalent multispecific antibody in which the Fab domains (a) bind to two distinct target epitopes that are within a proximity of 60-120 angstroms from each other (thus allowing simultaneous binding), and (b) have monovalent binding affinities or effective affinities (K_D) that range from about 100 nM to about 100 pM.

[0106] The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. For example, a monoclonal antibody can be an antibody that is derived from a single clone, including any eukaryotic, prokaryotic, or phage clone, and not the method by which it is produced. A monoclonal antibody composition displays a single binding specificity and affinity for a particular epitope. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to conventional (polyclonal) antibody preparations which typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. The modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. Monoclonal antibodies can be prepared using a wide variety of techniques known in the art including, e.g., but not limited to, hybridoma, recombinant, and phage display technologies. For example, the monoclonal antibodies to be used in accordance with the present methods may be made by the hybridoma method first described by Kohler et al., *Nature* 256:495 (1975), or may be made by recombinant DNA methods (See, e.g., U.S. Pat. No. 4,816,567). The "monoclonal antibodies" may also be isolated from phage antibody libraries using the techniques described in Clackson et al., *Nature* 352:624-628 (1991) and Marks et al., *J. Mol. Biol.* 222:581-597 (1991), for example.

[0107] As used herein, the term "pharmaceutically-acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal compounds, isotonic and absorption delaying compounds, and the like, compatible with pharmaceutical administration. Pharmaceutically-acceptable carriers and their formulations are known to one skilled in the art and are described, for example, in Remington's Pharmaceutical Sciences (20^{th} edition, ed. A. Gennaro, 2000, Lippincott, Williams & Wilkins, Philadelphia, Pa.).

[0108] As used herein, the term "polyclonal antibody" means a preparation of antibodies derived from at least two (2) different antibody-producing cell lines. The use of this term includes preparations of at least two (2) antibodies that contain antibodies that specifically bind to different epitopes or regions of an antigen.

[0109] As used herein, the term "polynucleotide" or "nucleic acid" means any RNA or DNA, which may be unmodified or modified RNA or DNA. Polynucleotides include, without limitation, single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, RNA that is mixture of single- and double-stranded regions, and hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, polynucleotide refers to triple-stranded regions comprising RNA or DNA or both RNA and DNA. The term polynucleotide also includes DNAs or RNAs containing one or more modified bases and DNAs or RNAs with backbones modified for stability or for other reasons.

[0110] As used herein, the terms "polypeptide", "peptide" and "protein" are used interchangeably herein to mean a polymer comprising two or more amino acids joined to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres. Polypeptide refers to both short chains, commonly referred to as peptides, glycopeptides or oligomers, and to longer chains, generally referred to as proteins. Polypeptides may contain amino acids other than the 20 gene-encoded amino acids. Polypeptides include amino acid sequences modified either by natural processes, such as post-translational processing, or by chemical modification techniques that are well known in the art. Such modifications are well described in basic texts and in more detailed monographs, as well as in a voluminous research literature.

[0111] As used herein, the term "recombinant" when used with reference, e.g., to a cell, or nucleic acid, protein, or vector, indicates that the cell, nucleic acid, protein or vector, has been modified by the introduction of a heterologous nucleic acid or protein or the alteration of a native nucleic acid or protein, or that the material is derived from a cell so modified. Thus, for example, recombinant cells express genes that are not found within the native (non-recombinant) form of the cell or express native genes that are otherwise abnormally expressed, under expressed or not expressed at all.

[0112] As used herein, the term "separate" therapeutic use refers to an administration of at least two active ingredients at the same time or at substantially the same time by different routes.

[0113] As used herein, the term "sequential" therapeutic use refers to administration of at least two active ingredients at different times, the administration route being identical or different. More particularly, sequential use refers to the whole administration of one of the active ingredients before administration of the other or others commences. It is thus possible to administer one of the active ingredients over several minutes, hours, or days before administering the other active ingredient or ingredients. There is no simultaneous treatment in this case.

[0114] As used herein, "specifically binds" refers to a molecule (e.g., an antibody or antigen binding fragment thereof) which recognizes and binds another molecule (e.g., an antigen), but that does not substantially recognize and bind other molecules. The terms "specific binding," "specifically binds to," or is "specific for" a particular molecule (e.g., a polypeptide, or an epitope on a polypeptide), as used herein, can be exhibited, for example, by a molecule having a K_D for the molecule to which it binds to of about 10^{-4} M, 10^{-5} M, 10^{-6} M, 10^{-7} M, 10^{-8} M, 10^{-9} M, 10^{-10} M, 10^{-11} M, or 10^{-12} M. The term "specifically binds" may also refer to binding where a molecule (e.g., an antibody or antigen binding fragment thereof) binds to a particular polypeptide, or an epitope on a particular polypeptide, without substantially binding to any other polypeptide, or polypeptide epitope.

[0115] As used herein, the term "simultaneous" therapeutic use refers to the administration of at least two active ingredients by the same route and at the same time or at substantially the same time.

[0116] As used herein, the term "therapeutic agent" is intended to mean a compound that, when present in an effective amount, produces a desired therapeutic effect on a subject in need thereof.

[0117] "Treating" or "treatment" as used herein covers the treatment of a disease or disorder described herein, in a subject, such as a human, and includes: (i) inhibiting a disease or disorder, i.e., arresting its development; (ii) relieving a disease or disorder, i.e., causing regression of the disorder; (iii) slowing progression of the disorder; and/or (iv) inhibiting, relieving, or slowing progression of one or more symptoms of the disease or disorder. In some embodiments, treatment means that the symptoms associated with the disease are, e.g., alleviated, reduced, cured, or placed in a state of remission.

[0118] It is also to be appreciated that the various modes of treatment of disorders as described herein are intended to mean "substantial," which includes total but also less than total treatment, and wherein some biologically or medically relevant result is achieved. The treatment may be a continuous prolonged treatment for a chronic disease or a single, or few time administrations for the treatment of an acute condition.

Heterodimeric Trivalent/Tetravalent Multispecific Antibodies of the Present Technology

[0119] The heterodimeric trivalent/tetravalent multispecific antibodies of the present technology can bind simultaneously to three or four targets that have a distinct structure, e.g., 3-4 different target antigens, 3-4 different epitopes on the same target antigen, or a combination of haptens and target antigens or epitopes on a target antigen. A variety of HDTVS antibodies can be produced using molecular engineering. For example, the HDTVS antibodies disclosed herein utilize combinations of the full immunoglobulin framework (e.g., IgG), and single chain variable fragments (scFvs).

[0120] HDTVS antibodies can be made, for example, by combining and/or engineering heavy chains and/or light chains that recognize different epitopes of the same or different antigen. In some embodiments, the HDTVS protein is trivalent and tri-specific, comprising, for example, an immunoglobulin (e.g., IgG) with a binding site for a first antigen (one V_H/V_L pair) and a binding site for a second antigen (a different V_H/V_L pair) and an scFv for a third antigen. In some embodiments, the HDTVS protein is trivalent and bispecific, comprising, for example, an immunoglobulin (e.g., IgG) with two binding sites (two V_H/V_L pairs) for a first antigen, and a scFv for a second antigen. In some embodiments, the HDTVS protein is tetravalent and tri-specific, comprising, for example, an immunoglobulin (e.g., IgG) with a binding site for a first antigen (one V_H/V_L pair) and a binding site for a second antigen (a different V_H/V_L pair) and two identical scFvs for a third antigen. In some embodiments, the HDTVS protein is tetravalent and tri-specific, comprising, for example, an immunoglobulin (e.g., IgG) with two binding sites (two V_H/V_L pairs) for a first antigen, an scFv for a second antigen and an scFv for a third antigen. In some embodiments, the HDTVS protein is tetravalent and tetra-specific, comprising, for example, an immunoglobulin (e.g., IgG) with a binding site for a first antigen (one V_H/V_L pair) and a binding site for a second antigen (different V_H/V_L pair), an scFv for a third antigen and an scFv for a fourth antigen.

[0121] In some embodiments, at least one scFv of the HDTVS antibodies of the present technology binds to an antigen or epitope of a B-cell, a T-cell, a myeloid cell, a plasma cell, or a mast-cell. Additionally or alternatively, in certain embodiments, at least one scFv of the HDTVS antibodies of the present technology binds to an antigen selected from the group consisting of Dabigatran, a4, a4b7, a4b7+aEb7, a5, AXL, BnDOTA, CD11a (LFA-1), CD3, CD4, CD8, CD16, CD19, CD22, CD23, CD25, CD28, CD30 (TNFRSF8), CD33, CD38, CD40, CD40L, CD47, CD49b (a2), CD54 (ICAM-1), CD56, CD74, CD80, CD115 (CSF1R), CD116a (CSF2Ra), CD123, CD134 (OX40), CD137 (41BB), CD152 (CTLA4), CD184 (CXCR4), CD192 (CCR2), CD194 (CCR4), CD195 (CCR5), CD223 (LAG-3), CD252 (OX40L), CD254 (RANKL), CD262 (DR5), CD27, CD200, CD221 (IGF1R), CD248, CD274 (PD-L1), CD275 (ICOS-L), CD278 (ICOS), CD279 (PD-1), CD319 (SLAMF7), CD371 (CLEC12A), MADCAM1, MT1-MMP (MMP14), NKG2A, NRP1,TIGIT, VSIR, KIRDL1/2/3, and KIR2DL2.

[0122] Additionally or alternatively, in certain embodiments, the HDTVS antibodies disclosed herein are capable of binding to cells (e.g., tumor cells) that express a cell surface antigen selected from the group consisting of a2b b3 (Glycoprotein IIb/IIIa), a4, a4b7, a4b7 +aEb7, a5, Activin receptor type-2B, ALK1, Alpha-synuclein, amyloid beta, APP, AXL, Blood Group A, CAIX, CCL-2, CD105 (endoglin), CD115 (CSF1R), CD116a (CSF2Ra), CD123, CD152 (CTLA4), CD184 (CXCR4), CD19, CD192 (CCR2), CD194 (CCR4), CD195 (CCR5), CD20, CD200, CD22,

CD221 (IGF1R), CD248, CD25, CD25? (BAFF), CD26, CD262 (DR5), CD276 (B7H3), CD3, CD30 (TNFRSF8), CD319 (SLAMF7), CD33, CD332 (FGFR2), CD350 (FZD10), CD37, CD371 (CLEC12A), CD38, CD4, CD49b (a2), CD51 (a5), CD52, CD56, CD61 (a4b3), CD70, CD73 (NTSE), CD74, CEA, Claudin-18.2, cMET, CRLR, DLL3, DLL4, DNA/histone (H1) complex, EGFR, EpCAM, EGFR-HER3, EGFRvIII, EphA3, ERGT(GalNAc) Tn Antigen, FLT1, FOLR1, frizzled family receptor (FZD), Lewis Y, Lewis X, GCGR, GD2, GD2 α-acetyl, GD3, GM1, GM1 fucosyl, GM2, GPA33, GPNMB, GUCY2C, HER2, HER3, HGFR (cMET), IgHe, IGLF2, Kallikreins, LINGO1, LOXL2, Ly6/PLAUR domain-containing protein 3, MADCAM1, MAG, Mesothelin, MT1-MMP (MMP14), MUC1, Mucin SAC, *NaPi*2b, NeuGc-GM3, notch, NOTCH2/NOTCH3 receptors, oxLDL, P-selectin, PCSK9, PDGFRA, PDGFRa, phosphatidylserine, polysialic acid, PSMA, PVRL4, RGMA, CD240D Blood group D antigen, root plate-specific spondin 3, serum amyloid P component, STEAP-1, TACSTD2, TGFb, TWEAKR, TYRP1, VEGFR2, VSIR, CD171 (L1CAM), CD19, CD47, pMHC [NY-ESO1], pMHC[MART1], pMHC[MAGEA1], pMHC [Tyrosinase], pMHC[gp100], pMHC[MUC1], pMHC[tax], pMHC[WT-1], pMHC[EBNA-1], pMHC[LMP2], pMHC [hTERT], GPC3, CD80, CD23, and fibronectin extra domain-B.

[0123] Methods for producing the HDTVS antibodies of the present technology include engineered recombinant monoclonal antibodies which have additional cysteine residues so that they crosslink more strongly than the more common immunoglobulin isotypes. See, e.g., FitzGerald et al., *Protein Eng.* 10(10):1221-1225 (1997). HDTVS recombinant fusion proteins can be engineered by linking two or more different single-chain antibody or antibody fragment segments with the needed dual specificities. See, e.g., Coloma et al., Nature Biotech. 15:159-163 (1997).

[0124] Recombinant methods can be used to produce a variety of fusion proteins. In some embodiments, a HDTVS antibody according to the present technology comprises an immunoglobulin, which immunoglobulin comprises two heavy chains and two light chains, and two scFvs, wherein each scFv is linked to the C-terminal end of one of the two light chains of any immunoglobulin disclosed herein. In various embodiments, scFvs are linked to the light chains via a linker sequence. In some embodiments, a linker is at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100 or more amino acids in length.

[0125] In some embodiments, a linker is characterized in that it tends not to adopt a rigid three-dimensional structure, but rather provides flexibility to the polypeptide (e.g., first and/or second antigen binding sites). In some embodiments, a linker is employed in a HDTVS antibody described herein based on specific properties imparted to the HDTVS antibody such as, for example, an increase in stability. In some embodiments, a HDTVS antibody of the present technology comprises a G_4S linker (SEQ ID NO: 2508). In certain embodiments, a HDTVS antibody of the present technology comprises a $(G_4S)_n$ linker, wherein n is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 1 1, 12, 13, 14, 15 or more (SEQ ID NO: 2509).

[0126] Exemplary V_H and V_L amino acid sequences that may be employed in the HDTVS antibodies of the present technology are provided in Table 1.

TABLE 1

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
a2b b3 (Glyco-protein IIb/ IIIa)	DILMTQSPSSM SVSLGDTVSIT CHASQGISSNI GWLQQKPGKS FMGLIYYGTN LVDGVPSRFS GSGSGADYSL TISSLDSEDFA DYYCVQYAQ LPYTFGGGTK LEIK	1	QGIS SN	2	YGT	3	VQY AQLP YT	4	EVQLQQSGAELV KPGASVKLSCTA SGFNIKDTYVHW VKQRPEQGLEWI GRIDPANGYTKY DPKFQGKATITA DTSSNTAYLQLS SLTSEDTAVYYC VRPLYDYYAMD YWGQGTSVTVSS	5	GFNI KDT Y	6	IDPA NGYT	7	VRPL YDYY AMDY	8
a2b b3 (Glyco-protein IIb/ IIIa)	DIQMTQTPSTL SASVGDRVTIS CRASQDINNY LNWYQQKPG KAPKLLIYYTS TLHSGVPSRFS GSGSGTDYTL TISSLQPDDFA TYFCQQGNTL PWTFGQGTKV EVK	9	QDIN NY	10	YTS	11	QQG NTLP WT	12	QVQLVQSGAEV KKPGSSVKVSCK ASGYAFTNYLIE WVRQAPGQGLE WIGVIYPGSGGT NYNEKFKGRVTL TVDESTNTAYME LSSLRSEDTAVY FCARRDGNYGWF AYWGQGTLVTV SS	13	GYA FTNY L	14	IYPG SGGT	15	ARRD GNYG WFAY	16
a4	DIQMTQSPSSL SASVGDRVTIT CKTSQDINKY MAWYQQTPG KAPRLLIHYTS ALQPGIPSRFS GSGSGRDYTF TISSLQPEDIA TYYCLQYDNL WTFGQGTKVE IK	17	QDIN KY	18	YTS	19	LQY DNL WT	20	QVQLVQSGAEV KKPGASVKVSCK ASGFNIKDTYIH WVRQAPGQRLE WMGRIDPANGY TKYDPKFQGRVT ITADTSASTAYM ELSSLRSEDEAV YYCAREGYYGN YGVYAMDYWG QGTLVTVSS	21	GFNI KDT Y	22	IDPA NGYT	23	AREG YYGN YGVY AMDY	24
a4b7	DVVMTQSPLS LPVTPGEPASI SCRSSQSLAKS YGNTYLSWYL QKPGQSPQLLI YGISNRFSGVP DRFSGSGSGT DFTLKISRVEA EDVGVYYCLQ GTHQPYTFGQ GTKVEIK	25	QSLA KSYG NTY	26	GIS	27	LQGT HQP YT	28	QVQLVQSGAEV KKPGASVKVSCK GSGYTFTSYWM HWVRQAPGQRL EWIGEIDPSESN TNYNQKFKGRVT LTVDISASTAYM ELSSLRSEDTAV YYCARGGYDGWD YAIDYWGQGTL VTVSS	29	GYTF TSY W	30	IDPS ESNT	31	ARGG YDGW DYAI DY	32

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
a4b7 + aEb7	DIQMTQSPSSL SASVGDRVTIT CRASESVDDL LHWYQQKPG KAPKLLIKYAS QSISGVPSRFS GSGSGTDFTLT ISSLQPEDFAT YYCQQGNSLP NTFGQGTKVE IK	33	ESVD DL	34	YAS Q	35	QQG NSLP NT	36	EVQLVESGGGLV QPGGSLRLSCAA SGFFITNNYWGW VRQAPGKGLEW VGYISYSGSTSY NPSLKSRFTISR DTSKNTFYLQMN SLRAEDTAVYYC ARTGSSGYFDFW GQGTLVTVSS	37	GFFI TNN Y	38	ISYS GST	39	ARTG SSGY FDF	40
a5	EIVLTQSPATL SLSPGERATLS CRASQSVSSY LAWYQQKPG QAPRLLIYDAS NRATGIPARFS GSGSGTDFTLT ISSLEPEDFAV YYCQQRSNWP PFTFGPGTKV DIK	41	QSVS SY	42	DAS	43	QQRS NWP PFT	44	QVQLVESGGGV VQPGRSRRLSCA ASGFTFSRYTMH WVRQAPGKGLE WVAVISFDGSNK YYVDSVKGRFTI SRDNSENTLYLQ VNILRAEDTAVY YCAREARGSYAF DIWGQGTMVTV SS	45	GFTF SRYT	46	ISFD GSNK	47	AREA RGSY AFDI	48
Activin recep-tor type-2B	QSALTQPASV SGSPGQSITIS CTGTSSDVGSY NYVNWYQQH PGKAPKLMIY GVSKRPSGVS NRFSGSKSGN TASLTISGLQA EDEADYYCGT FAGGSYYGVF GGGTKLTVL	49	SSDV GSYN Y	50	GVS	51	GTFA GGS YYG V	52	QVQLVQSGAEV KKPGASVKVSCK ASGYTFTSSYIN WVRQAPGQGLE WMGTINPVSGST SYAQKFQGRVT MTRDTSISTAYM ELSRLRSDDTAV YYCARGGWFDY WGQGTLVTVSS	53	GYTF TSSY	54	INPV SGST	55	ARGG WFDY	56
ALK1	EIVLTQSPGTL SLSPGERATLS CRASQSVSSSY LAWYQQKPG QAPRLLIYGTS SRATGIPDRFS GSGSGTDFTLT ISRLEPEDFAV YYCQQYGSSPI TFGQGTRLEIK	57	QSVS SSY	58	GTS	59	QQY GSSP IT	60	QVQLQESGPGLV KPSQTLSLTCTV SGGSISSGEYYW NWIRQHPGKGLE WIGYIYYSGSTY YNPSLKSRVTIS VDTSKNQFSLKL SSVTAADTAVYY CARESVAGFDYW GQGTLVTVSS	61	GGSI SSGE YY	62	IYYS GST	63	ARES VAGF DY	64

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
Alpha-synuclein	DIQMTQSPSSLSASVGDRVTITCKSIQTLLYSSNQKNYLAWFQQKPGKAPKLLIYWASIRKSGVPSRFSGSGSGTDFTLTISSLQPEDLATYYCQQYYSYPLTFGGGTKLEIK	65	QTLLYSSNQKNY	66	WAS	67	QQYYSYPLT	68	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYGMSWVRQAPGKGLEWVASISSGGGSTYYPDNVKGRFTISRDDAKNSLYLQMNSLRAEDTAVYYCARGGAGIDYWGQGTLVTVSS	69	GFTFSNYG	70	ISSGGGST	71	ARGGAGIDYW	72
amyloid beta	DVVMTQSPLSLPVTPGEPASISCKSSQSLLDSDGKTYLNWLLQKPGQSPQRLIYLVSKLDSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCWQGTHFPRTFGQGTKVEIK	73	QSLLDSDGKTY	74	LYS	75	WQGTHFPRT	76	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYGMSWVRQAPGKGLEWVASIRSGGGRTYYSDNVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCVRYDHYSGSSDYWGQGTLVTVSS	77	GFTFSNYG	78	IRSGGGRT	79	VRYDHYSGSSDY	80
amyloid beta	DVVMTQSPLSLPVTLGQPASISCRSSQSLIYSDGNAYLHWFLQKPGQSPRLLIYKVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCSQSTHVPWTFGQGTKVEIK	81	qSLIYSDGNAY	82	KVS	83	SQSTHVPWT	84	EVQLVESGGGLVQPGGSLRLSCAASGFTFSRYSMSWVRQAPGKGLELVAQINSVGNSTYYPDTVKGRFTISRDNAKNTLYLQMNSLRAEDTAVYYCASGDYWGQGTLVTVSS	85	GFTFSRYS	86	INSVGNST	87	ASGDY	88
amyloid beta	DIVMTQSPLSLPVTPGEPASISCRSSQSLVYSNGDTYLHWYLQKPGQSPQLLIYKVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCSQSTHVPWTFGQGTKVEIK	89	QSLVYSNGDTY	90	KVS	91	SQSTHVPWT	92	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYGMSWVRQAPGKGLELVASINSNGGSTYYPDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCASGDYWGQGTTVTVSS	93	GFTFSSYG	94	INSNGGST	95	ASGDYW	96

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
amyloid beta	DVVMTQSPLS LPVTLGQPASI SCKSSQSLLYS DAKTYLNWF QQRPGQSPRR LIYQISRLDPG VPDRFSGSGS GTDFTLKISRV EAEDVGVYYC LQGTHYPVLF GQGTRLEIK	97	QSLL YSD AKTY	98	QIS	99	LQGT HYP VL	100	QVQLVQSGAEV KKPGASVKVSCK ASGYYTEAYYIH WVRQAPGQGLE WMGRIDPATGNT KYAPRLQDRVT MTRDTSTSTVYM ELSSLRSEDTAV YYCASLYSLPVY WGQGTTVTVSS	101	GYY TEA YY	102	IDPA TGNT	103	ASLY SLPV Y	104
amyloid beta	DIQMTQSPSSL SASVGDRVTIT CRASQSISSYL NWYQQKPGK APKLLIYAASS LQSGVPSRFSG SGSGTDFTLTI SSLQPEDFATY YCQQSYSTPL TFGGGTKVEI K	105	QSIS SY	106	AAS	107	QQS YSTP LT	108	QVQLVESGGGV VQPGRSLRLSCA ASGFAFSSYGMH WVRQAPGKGLE WVAVIWFDGTK KYYTDSVKGRFT ISRDNSKNTLYL QMNTLRAEDTA VYYCARDRGIGA RRGPYYMDVWG KGTTVTVSS	109	GFAF SSYG	110	IWFD GTKK	111	ARDRG IGARR GPYYM DV	112
APP	DIVLTQSPATL SLSPGERATLS CRASQSVSSSY LAWYQQKPG QAPRLLIYGAS SRATGVPARF SGSGSGTDFTL TISSLEPEDFA TYYCLQIYNM PITFGQGTKVE IK	113	QSVS SSY	114	GAS	115	LQIY NMPI T	116	QVELVESGGGLV QPGGSLRLSCAA SGFTFSSYAMSW VRQAPGKGLEW VSAINASGTRTY YADSVKGRFTIS RDNSKNTLYLQ MNSLRAEDTAV YYCARGKGNTH KPYGYVRYFDV WGQGTLVTVSS	117	GFTF SSYA	118	INAS TRT	119	ARGKG GNTH KPYG YVRY FDV	120
AXL	EIVLTQSPGTL SLSPGERATLS CRASQSVSSSY LAWYQQKPG QAPRLLIYGAS SRATGIPDRFS GSGSGTDFTLT ISRLEPEDFAV YYCQQYGSSP YTFGQGTKLEI K	121	QSVS SSY	122	GAS	123	QQY GSSP YT	124	EVQLLESGGGLV QPGGSLRLSCAA SGFTFSSYAMNW VRQAPGKGLEW VSTTSGSGASTY YADSVKGRFTIS RDNSKNTLYLQ MNSLRAEDTAV YYCAKIWIAFDI WGQGTMVTVSS	125	GFTF SSYA	126	TSGS GAST	127	AKIWI AFDI	128

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
Blood group A	DIQMTQTTSSL SASLGDRVTIS CRASQDINNY LNWYQQKPD GTVKLLIHYTS RLHSGVPSRFS GSGSGTDYSL TISNLEQEDIA TYFCQQGNTL PWTFGGGTKL EIK	129	QDIN NY	130	YTS	131	QQG NTLP WT	132	QVQLQQPGAELV KPGTSVKLSCKA SGYNFTSYWINW VKLRPGQGLEWI GDIYPGSGITNY NEKFKSKATLTV DTSSSTAYMQLS SLASEDSALYYC AGQYGNLWFAYW GQGTLVTVSS	133	GYN FTSY W	134	IYPG SGIT	135	AGQY GNLW FAY	136
BnDOTA	QAVVIQESAL TTPPGETVTLT CGSSTGAVTA SNYANWVQE KPDHCFTGLIG GHNNRPPGVP ARFSGSLIGDK AALTIAGTQTE DEAIYFCALW YSDHWVIGGG TRLTVL	137	TGAV TASN Y	138	GHN	139	ALW YSD HWV IGGG	140	HVKLQESGPGLV QPSQSLSLTCTV SGFSLTDYGVHW VRQSPGKGLEWL GVIWSGGGTAYN TALISRLNIYRD NSKNQVFLEMNS LQAEDTAMYYCA RRGSYPYNYFDA WGCGTTVTVSS	141	GFSL TDY G	142	IWSG GGT	143	ARRG SYPY NYFD A	144
CAIX	DIVMTQSQRF MSTTVGDRVS ITCKASQNVV SAVAWYQQK PGQSPKLLIYS ASNRYTGVPD RFTGSGSGTDF TLTISNMQSED LADFFCQQYS NYPWTFGGGT KLEIK	145	QNVV SA	146	SAS	147	QQY SNYP WT	148	DVKLVESGGGLV KLGGSLKLSCAA SGFTFSNYYMSW VRQTPEKRLELV AAINSDGGITYY LDTVKGRFTISR DNAKNTLYLQMS SLKSEDTALFYC ARHRSGYFSMDY WGQGTSVTVSS	149	GFTF SNY Y	150	INSD GGIT	151	ARHR SGYF SMDY	152
CCL-2	EIVLTQSPATL SLSPGERATLS CRASQSVSDA YLAWYQQKP GQAPRLLIYD ASSRATGVPA RFSGSGSGTDF TLTISSLEPED FAVYYCHQYIQ LHSFTFGQGT KVEIK	153	QSVS DAY	154	DAS	155	HQYI QLHS FT	156	QVQLVQSGAEV KKPGSSVKVSCK ASGGTFSSYGIS WVRQAPGQGLE WMGGIIPIFGTA NYAQKFQGRVTI TADESTSTAYME LSSLRSEDTAVY YCARYDGIYGEL DFWGQGTLVTVS S	157	GGTF SSYG	158	IIPI FGTA	159	ARYD GIYG ELDF	160

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
CD105 (endo-glin)	QIVLSQSPAIL SASPGEKVTMT CRASSSVSYM HWYQQKPGSS PKPWIYATSN LASGVPVRFS GSGSGTSYSLT ISRVEAEDAAT YYCQQWSSNP LTFGAGTKLE LK	161	SSVS Y	162	ATS	163	QQW SSNP LT	164	EVKLEESGGGLV QPGGSMKLSCAA SGFTFSDAWMD WVRQSPEKGLE WVAEIRSKASNH ATYYAESVKGRF TISRDDSKSSVY LQMNSLRAEDTG IYYCTRWRRFFD SWGQGTTLTVSS	165	GFTF SDA W	166	IRSK ASNH AT	167	TRWR RFFD S	168
CD115 (CSF1R)	EIVLTQSPATL SLSPGERATLS CKASQSVDYD GDNYMNWYQ QKPGQAPRLLI YAASNLESGIP ARFSGSGSGT DFTLTISSLEP EDFAVYYCHLS NEDLSTFGGG TKVEIK	169	QSVD YDGD NY	170	AAS	171	HLSN EDLS T	172	QVQLVQSGAEV KKPGSSVKVSCK ASGYTFTDNYMI WVRQAPGQGLE WMGDINPYNGG TTFNQKFKGRVT ITADKSTSTAYM ELSSLRSEDTAV YYCARESPYFSN LYVMDYWGQGT LVTVSS	173	GYTF TDN Y	174	INPY NGGT	175	ARES PYFS NLYV MDYW	176
CD116a (CSF2 Ra)	QSVLTQPPSVS GAPGQRVTISC TGSGSNIGAPY DVSWYQQLPG TAPKLLIYHN NKRPSGVPDR FSGSKSGTSAS LAITGLQAEDE ADYYCATVEA GLSGSVFGGG TKLTVL	177	GSNI GAPY D	178	HNN	179	ATVE AGLS GSV	180	QVQLVQSGAEV KKPGASVKVSCK VSGYTLTELSIH WVRQAPGKGLE WMGGFDPEENEI VYAQRFQGRVT MTEDTSTDTAY MELSSLRSEDTA VYYCAIVGSFSP LTLGLWGQGTMV TVSS	181	GYT LTEL S	182	FDPE ENEI	183	AIVG SFSP LTLG L	184
CD11a (LFA-1)	DIQMTQSPSSL SASVGDRVTIT CRASKTISKYL AWYQQKPGK APKLLIYSGST LQSGVPSRFSG SGSGTDFTLTI SSLQPEDFATY YCQQHNEYPL TFGQGTKVEI K	185	KTISKY	186	SGS	187	QQH NEYP LT	188	EVQLVESGGGLV QPGGSLRLSCAA SGYSFTGHWMN WVRQAPGKGLE WVGMIHPSDSET RYNQKFKDRFTI SVDKSKNTLYLQ MNSLRAEDTAV YYCARGIYFYGT TYFDYWGQGTL VTVSS	189	GYSF TGH W	190	IHPS DSET	191	ARGI YFYG TTYF DYW	192

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
CD123	DFVMTQSPSS LTVTAGEKVT MSCKSSQSLL NSGNQKNYLT WYLQKPGQPP KLLIYWASTR ESGVPDRFTGS GSGTDFTLTIS SVQAEDLAVY YCQNDYSYPY TFGGGTKLEIK	193	QSLL NSGN QKNY	194	WAS	195	QND YSYP YT	196	EVQLQQSGPELV KPGASVKMSCK ASGYTFTDYYM KWVKQSHGKSL EWIGDIIPSNGA TFYNQKFKGKAT LTVDRSSSTAYM HLNSLTSEDSAV YYCTRSHLLRAS WFAYWGQGTLVT VSA	197	GYTF TDY Y	198	IIPS N GAT	199	TRSH LLRA SWFA Y	200
CD123	QAVVTQEPSL TVSPGGTVTL TCRSSTGAVT TSNYANWVQ QKPGQAPRGL IGGTNKRAPW TPARFSGSLLG GKAALTITGA QAEDEADYYC ALWYSNLWV FGGGTKLTVL	201	TGAV TTSN Y	202	GTN	203	ALW YSNL WV	204	EVQLVESGGGLV QPGGSLRLSCAA SGFTFSTYAMNW VRQAPGKGLEW VGRIRSKYNNYA TYYADSVKDRFT ISRDDSKNSLYL QMNSLKTEDTAV YYCVRHGNFGNS YVSWFAYWGQGT LVTVSS	205	GFTF STYA	206	IRSK YNNY AT	207	VRHG NPGN SYVS WFAY	208
CD134 (OX40)	DIQMTQSPSSL SASVGDRVTIT CRASQDISNYL NWYQQKPGK APKLLIYYTSR LRSGVPSRFSG SGSGTDFTLTI SSLQPEDFATY YCQQGHTLPP TFGQGTKVEI K	209	QDIS NY	210	YTS	211	QQG HTLP PT	212	EVQLVQSGAEVK KPGASVKVSCKA SGYTFTDSYMSW VRQAPGQGLEWI GDMYPDNGDSS YNQKFRERVTIT RDTSTSTAYLEL SSLRSEDTAVYY CVLAPRWYFSVW GQGTLVTVSS	213	GYTF TDSY	214	MYPD NGDS	215	VLAP RWYF SVW	216
CD137 (41BB)	SYELTQPPSVS VSPGQTASITC SGDNIGDQYA HWYQQKPGQ SPVLVIYQDK NRPSGIPERFS GSNSGNTATL TISGTQAMDE ADYYCATYTG FGSLAVFGGG TKLTVL	217	NIGD QY	218	QDK	219	ATYT GFGS LAV	220	EVQLVQSGAEVK KPGESLRISCKG SGYSFSTYWISW VRQMPGKGLEWM GKIYPGDSYTNY SPSFQGQVTISA DKSISTAYLQWS SLKASDTAMYYC ARGYGIFDYWGQ GTLVTVSS	221	GYSF STY W	222	IYPG DSYT	223	ARGY GIFD Y	224

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
CD137 (41BB)	EIVLTQSPATL SLSPGERATLS CRASQSVSSY LAWYQQKPG QAPRLLIYDAS NRATGIPARFS GSGSGTDFTLT ISSLEPEDFAV YYCQQRSNWP PALTFCGGTK VEIK	225	QSVS SY	226	DAS	227	QQRS NWP PALT	228	QVQLQQWGAGL LKPSETLSLTCA VYGGSFSGYYWS WIRQSPEKGLEW IGEINHGGYVTY NPSLESRVTISV DTSKNQFSLKLS SVTAADTAVYYC ARDYGPGNYDWY FDLWGRGTLVTV SS	229	GGSF SGY Y	230	INHG GYV	231	ARDY GPGN YDWY FDL	232
CD152 (CTLA4)	DIQMTQSPSSL SASVGDRVTIT CRASQSINSYL DWYQQKPGK APKLLIYAASS LQSGVPSRFSG SGSGTDFTLTI SSLQPEDFATY YCQQYYSTPF TFGPGTKVEIK	233	QSIN SY	234	AAS	235	QQY YSTP FT	236	QVQLVESGGGV VQPGRSLRLSCA ASGFTFSSYGMH WVRQAPGKGLE WVAVIWYDGSN KYYADSVKGRFT ISRDNSKNTLYL QMNSLRAEDTA VYYCARDPRGAT LYYYYYGMDVW GQGTTVTVSS	237	GFTF SSYG	238	IWYD GSNK	239	ARDP RGAT LYYY YYGM DV	240
CD152 (CTLA4)	EIVLTQSPGTL SLSPGERATLS CRASQSVGSS YLAWYQQKP GQAPRLLIYG AFSRATGIPDR FSGSGSGTDFT LTISRLEPEDF AVYYCQQYGS SPWTFGQGTK VEIK	241	QSVGS SY	242	GAF	243	QQY GSSP WT	244	QVQLVESGGGV VQPGRSLRLSCA ASGFTFSSYTMH WVRQAPGKGLE WVTFISYDGNNK YYADSVKGRFTI SRDNSKNTLYLQ MNSLRAEDTAIY YCARTGWLGPFD YWGQGTLVTVSS	245	GFTF SSYT	246	ISYD GNNK	247	ARTG WLGP FDY	248
CD16	DTVLTQSPASL AVSLGQRATIS CKASQSVDFD GDSFMNWYQ QKPGQPPKLLI YTTSNLESGIP ARFSASGSGT DFTLNIHPVEE EDTATYYCQQ SNEDPYTFGG GTKLEIK	249	QSVD FDGD SF	250	TTS	251	QQS NEDP YT	252	QVTLKESGPGIL QPSQTLSLTCSF SGFSLRTSGMGV GWIRQPSGKGLE WLAHIWWDDDKR YNPALKSRLTIS KDTSSNQVFLKI ASVDTADTATYY CAQINPAWFAYW GQGTLVTVSA	253	GFSL RTSG MG	254	IWWD DDK	255	AQIN PAWF AY	256

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
CD184 (CXCR4)	DIQMTQSPSSL SASVGDRVTIT CRASQGISSW LAWYQQKPE KAPKSLIYAAS SLQSGVPSRFS GSGSGTDFTLT ISSLQPEDFVT YYCQQYNSYP RTFGQGTKVEI K	257	QGIS SW	258	AAS	259	QQY NSYP RT	260	EVQLVESGGGLV QPGGSLRLSCAA AGFTFSSYSMNW VRQAPGKGLEW VSYISSRSRTIY YADSVKGRFTIS RDNAKNSLYLQM NSLRDEDTAVYY CARDYGGQPPYY YYYGMDVWGQ GTTVTVSS	261	GFTF SSYS	262	ISSR SRTI	263	ARDY GGQP PYYY YYGM DV	264
CD19	DIQMTQTTSSL SASLGDRVTIS CRASQDISKYL NWYQQKPDG TVKLLIYHTSR LHSGVPSRFSG SGSGTDYSLTI SNLEQE DIATYFCQQG NTLPYTFGGG TKLEIK	265	QDISK Y	266	HTS	267	QQG NTLP YT	268	EVKLQESGPGLV APSQSLSVTCTV SGVSLPDYGVSW IRQPPRKGLEWL GVIWGSETTYYN SALKSRLTIIKD NSKSQVFLK MNSLQTDDTAIY YCAKHYYYGGS YAMDYWGQGTS VTVSS	269	GVSL PDY G	270	IWGS ETT	271	AKHY YYGG SYAM DY	272
CD19	EIVLTQSPDFQ SVTPKEKVTIT CRASESVDTF GISFMNWFQQ KPDQSPKLLIH EASNQGSGVP SRFSGSGSGTD FTLTINSLEAE DAATYYCQQS KEVPFTFGGG TKVEIK	273	ESVDT FGISF	274	EAS	275	QQS KEVP FT	276	EVQLVESGGGLV QPGGSLRLSCAA SGFTFSSSWMNW VRQAPGKGLEW VGRIYPGDGDTN YNVKFKGRFTIS RDDSKNSLYLQM NSLKTEDTAVYY CARSGFITTVRD FDYWGQGTLVTV SS	277	GFTF SSSW	278	IYPG DGDT	279	ARSG FITT VRDF DY	280
CD19	DIQMTQSPSSL SASVGDSVTIT CQASTDISSHL NWYQQKPGK APELLIYYGSH LLSGVPSRFSG SGSGTDFTFTI SSLEAEDAAT YYCGQGNRLP YTFGQGTKVE IE	281	TDIS SH	282	YGS	283	GQG NRLP YT	284	QVQLQESGPGLV KPSETLSLTCAV SGHSISHDHAWS WVRQPPGEGLEW IGFISYSGITNY NPSLQGRVTISR DNSKNTLYLQMN SLRAEDTAVYYC ARSLARTTAMDY WGEGTLVTVSS	285	GHSI SHD HA	286	ISYS GIT	287	ARSL ARTT AMDY	288

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
CD19	EIVLTQSPATL SLSPGERATLS CSASSSVSYM HWYQQKPGQ APRLLIYDTSK LASGIPARFSG SGSGTDFTLTI SSLEPEDVAV YYCFQGSVYP FTFGQGTKLEI K	289	SSVS Y	290	DTS	291	FQGS VYPF T	292	QVQLQESGPGLV KPSQTLSLTCTV SGGSISTSGMGV GWIRQHPGKGLE WIGHIWWDDDK RYNPALKSRVTI SVDTSKNQFSLK LSSVTAADTAVY YCARMELWSYYF DYWGQGTLVTV SS	293	GGSI STSG MG	294	IWWD DDK	295	ARME LWSY YFDY	296
CD19	DIQLTQSPASL AVSLGQRATIS CKASQSVDYD GDSYLNWYQ QIPGQPPKLLI YDASNLVSGIP PRFSGSGSGTD FTLNIHPVEKV DAATYHCQQS TEDPWTFGGG TKLEIK	297	QSVD YDGD SY	298	DAS	299	QQST EDP WT	300	QVQLQQSGAELV RPGSSVKISCKA SGYAFSSYWMNW VKQRPGQGLEWI GQIWPGDGDTNY NGKFKGKATLTA DESSSTAYMQLS SLASEDSAVYFC ARRETTTVGRYY YAMDYWGQGTT VTVSS	301	GYA FSSY W	302	IWPG DGDT	303	ARRE TTTV GRYY YAMD Y	304
CD19	DIVMTQAAPSI PVTPGESVSIS CRSSKSLLNSN GNTYLYWFLQ RPGQSPQLLIY RMSNLASGVP DRFSGSGSGT AFTLRISRVEA EDVGVYYCM QHLEYPLTFG AGTKLEIK	305	KSLL NSNG NTY	306	RMS	307	MQH LEYP LT	308	QVQLQQSGPELI KPGASVKMSCK ASGYTFTSYVMH WVKQKPGQGLE QIGYINPYNDGT KYNEKFKGKATL TSDKSSTAYMEL SSLTSEDSAVYY CARGTYYYGSRV FDYWGQGTTLT VTVSS	309	GYTF TSYV	310	INPY NDGT	311	ARGT YYYG SRVF DY	312
CD19	EIVLTQSPAIM SASPGERVTM TCSASSGVNY MHWYQQKPG TSPRRWIYDTS KLASGVPARF SGSGSGTDYS LTISSMEPEDA ATYYCHQRGS YTFGGGTKLEI K	313	SGVN Y	314	DTS	315	HQR GSYT	316	QVQLVQPGAEV VKPGASVKLSCK TSGYTFTSNWMH WVKQAPGQGLE WIGEIDPSDSYT NYNQNFQGKAKL TVDKSTSTAYME VSSLRSDDTAVY YCARGSNPYYYA MDYWGQGTSVT VSS	317	GYTF TSN W	318	IDPS DSYT	319	ARGS NPYY YAMD Y	320

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
CD192 (CCR2)	DVVMTQSPLS LPVTLGQPASI SCKSSQSLLDS DGKTFLNWFQ QRPGQSPRRLI YLVSKLDSGV PDRFSGSGSGT DFTLKISRVEA EDVGVYYCW QGTHFPYTFG QGTRLEIK	321	QSLL DSDG KTF	322	LVS	323	WQG THFP YT	324	EVQLVESGGGLV KPGGSLRLSCAA SGFTFSAYAMN WVRQAPGKGLE WVGRIRTKNNN YATYYADSVKD RFTISRDDSKNT LYLQMNSLKTED TAVYYCTTFYGN GVWGQGTLVTVS S	325	GFTF SAY A	326	IRTK NNNY AT	327	TTFY GNGV W	328
CD194 (CCR4)	DVLMTQSPLS LPVTPGEPASI SCRSSRNIVHI NGDTYLEWYL QKPGQSPQLLI YKVSNRFSGV PDRFSGSGSGT DFTLKISRVEA EDVGVYYCFQ GSLLPWTFGQ GTKVEIK	329	RNIV HING DTY	330	KVS	331	FQGS LLP WT	332	EVQLVESGGDLV QPGRSLRLSCAA SGFIFSNYGMSW VRQAPGKGLEW VATISSASTYSYY PDSVKGRFTISRD NAKNSLYLQMN SLRVEDTALYYC GRHSDGNFAFGY WGQGTLVTVSS	333	GFIF SNY G	334	ISSA STYS	335	GRHS DGNF AFGY	336
CD195 (CCR5)	DIVMTQSPLSL PVTPGEPASIS CRSSQRLLSSY GHTYLHWYL QKPGQSPQLLI YEVSNRFSGV PDRFSGSGSGT DFTLKISRVEA EDVGVYYCSQ STHVPLTFGQ GTKVEIK	337	QRLL SSYG HTY	338	EVS	339	SQST HVPL T	340	EVQLVESGGGLV KPGGSLRLSCAA SGYTFSNYWIGW VRQAPGKGLEWI GDIYPGGNYIRN NEKFKDKTTLSA DTSKNTAYLQM NSLKTEDTAVYY CGSSFGSNYVFA WFTYWGQGTLV TVSS	341	GYTF SNY W	342	IYPG GNYI	343	GSSF GSN YVFA WFTY W	344
CD20	EIVLTQSPATL SLSPGERATLS CRASQSVSSY LAWYQQKPG QAPRLLIYDAS NRATGIPARFS GSGSGTDFTLT ISSLEPEDFAV YYCQQRSNWP ITFGQGTRLEI K	345	QSVS SY	346	DAS	347	QQRS NWPI T	348	EVQLVESGGGLV QPGRSLRLSCAA SGFTFNDYAMH WVRQAPGKGLE WVSTISWNSGSI GYADSVKGRFTI SRDNAKKSLYLQ MNSLRAEDTALY YCAKDIQYGNYY YGMDVWGQGTT VTVSS	349	GFTF NDY A	350	ISWN SGSI	351	AKDI QYGN YYYG MDV	352

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
CD20	QIVLSQ-SPAILS ASPGEKVTMT CRASSSVSYM HWYQQKPGSS PKPWIYAPSNL ASGVPARFSG SGSGTSYSLTI SRVEAEDAAT YYCQQWSFNP PTFGAGTKLE LK	353	SSVS Y	354	APS	355	QQW SFNP PT	356	QAYLQQSGAELV RPGASVKMSCKA SGYTFTSYNMH WVKQTPRQGLE WIGAIYPGNGDT SYNQKFKGKATL TVDKSSSTAYMQ LSSLTSEDSAVYF CARVVYYSNSY WYFDVWGTGTT VTVSGPSVFPLAP SS	357	GYTF TSYN	358	IYPG NGDT	359	ARVV YYSN SYWY FDV	360
CD20	QIVLSQ-SPAILS ASPGEKVTMT CRASSSVSYM HWYQQKPGSS PKPWIYATSN LASGVPARFS GSGSGTSYSFT ISRVEAEDAAT YYCQQWTFNP PTFGGGTRLEI K	361	SSVS Y	362	ATS	363	QQW TFNP PT	364	QAYLQQSGAELV RPGASVKMSCKA SGYTFTSYNMH WVKQTPRQGLE WIGGIYPGNGDT SYNQKFKGKATL TVGKSSSTAYMQ LSSLTSEDSAVYF CARYDYNYAMD YWGQGTSVTVSS	365	GYTF TSYN	366	IYPG NGDT	367	ARYD YNYA MDY	368
CD20	QIVLSQ-SPAILS ASPGEKVTMT CRASSSVSYIH WFQQKPGSSP KPWIYATSNL ASGVPVRFSG SGSGTSYSLTI SRVEAEDAAT YYCQQWTSNP PTFGGGTKLEI K	369	SSVS Y	370	ATS	371	QQW TSNP PT	372	QVQLQQPGAELV KPGASVKMSCK ASGYTFTSYNMH WVKQTPGRGLE WIGAIYPGNGDT SYNQKFKGKATL TADKSSSTAYMQ LSSLTSEDSAVY YCARSTYYGGD WYFNVWGAGTT VTVSA	373	GYTF TSYN	374	IYPG NGDT	375	ARST YYGG DWYF NV	376
CD20	DIQLTQSPSSL SASVGDRVTM TCRASSSVSYI HWFQQKPGK APKPWIYATS NLASGVPVRF SGSGSGTDYT FTISSLQPE- DIA	377	SSVS Y	378	ATS	379	QQW TSNP PT	380	QVQLQQSGAEV KKPGSSVKVSCK ASGYTFTSYNMH WVKQAPGQGLE WIGAIYPGNGDT SYNQKFKGKATL TADESTNTAYME LSSLRSEDTAFYY	381	GYTF TSYN	382	IYPG NGDT	383	ARST YYGG DWYF DV	384

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
	TYYCQQWTSN PPTFGGGTKLE IK								CARSTYYGGDW YFDVWGQGTTV TVSS							
CD20	DIVMTQTPLSL PVTPGEPASIS CRSSKSLLHSN GITYLYWYLQ KPGQSPQLLIY QMSNLVSGVP DRFSGSGSGT DFTLKISRVEA EDVGVYYCA QNLELPYTFG GGTKVEIK	385	KSLL HSNG ITY	386	QMS	387	AQN LELP YT	388	QVQLVQSGAEV KKPGSSVKVSCK ASGYAFSYSWIN WVRQAPGQGLE WMGRIFPGDGDT DYNGKFKGRVTI TADKSTSTAYME LSSLRSEDTAVY YCARNVFDGYW LVYWGQGTLVT VSS	389	GYA FSYS W	390	IFPG DGDT	391	ARNV FDGY WLVY	392	
CD200	DIQMTQSPSSL SASIGDRVTIT CKASQDINSY LSWFQQKPGK APKLLIYRAN RLVDGVPSRF SGSGSGTDYT LTISSLQPEDF AVYYCLQYDE FPYTFGGGTK LEIK	393	QDIN SY	394	RAN	395	LQY DEFP YT	396	QVQLQQSGSELK KPGASVKISCKA SGYSFTDYIILWV RQNPGKGLEWIG HIDPYYGSSNYN LKFKGRVTITAD QSTTTAYMELSS LRSEDTAVYYCG RSKRDYFDYWG QGTTLTVSS	397	GYSF TDYI	398	IDPY YGSS	399	GRSK RDYF DYW	400	
CD22	DIQLTQSPSSL AVSAGENVTM SCKSSQSVLYS ANHKNYLAW YQQKPGQSPK LLIYWASTRES GVPDRFTGSG SGTDFTLTISR VQVEDLAIYY CHQYLSSWTF GGGTKLEIK	401	QSVL YSAN HKNY	402	WAS	403	HQY LSSW T	404	QVQLQESGAELS KPGASVKMSCK ASGYTFTSYWLH WIKQRPGQGLE WIGYINPRNDYT EYNQNFKDKATL TADKSSSTAYMQ LSSLTSEDSAVY YCARRDITTFYW GQGTTLTVSS	405	GYTF TSY W	406	INPR NDYT	407	ARRD ITTF Y	408	

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
CD221 (IGF1R)	DIQMTQFPSSL SASVGDRVTIT CRASQGIRND LGWYQQKPG KAPKRLIYAA SRLHRGVPSRF SGSGSGTEFTL TISSLQPEDFA TYYCLQHNSY PCSFGQGTKL EIK	409	QGIR ND	410	AAS	411	LQH NSYP CS	412	EVQLLESGGGLV QPGGSLRLSCTA SGFTFSSYAMNW VRQAPGKGLEW VSAISGSGGTTFY ADSVKGRFTISR DNSRTTLYLQMN SLRAEDTAVYYC AKDLGWSDSYY YYYGMDVWGQ GTTVTVSS	413	GFTF SSYA	414	ISGS GGTT	415	AKDL GWSD SYYY YYGM DV	416
CD221 (IGF1R)	DIQMTQSPSSL SASLGDRVTIT CRASQGISSYL AWYQQKPGK APKLLIYAKST LQSGVPSRFSG SGSGTDFTLTI SSLQPEDSATY YCQQYWTFPL TFGGGTKVEI K	417	QGIS SY	418	AKS	419	QQY WTFP LT	420	EVQLLQSGGGLV QPGGSLRLSCAA SGFMFSRYPMH WVRQAPGKGLE WVGSISGSGGAT PYADSVKGRFTIS RDNSKNTLYLQ MNSLRAEDTAV YYCAKDFYQILT GNAFDYWGQGT TVTVSS	421	GFM FSRY P	422	ISGS GGAT	423	AKDF YQIL TGNA FDY	424
CD221 (IGF1R)	QIVLTQSPAIM SASPGEKVTIT CSASSSVSYIH WFQQKPGTSP KVWIYGTSNL ASGVPARFTG SGSGTSYSLTI SRMEAEDAAT YYCQQRSSYP FTFGSGTKLEI K	425	SSVS Y	426	GTS	427	QQRS SYPF T	428	EVQLQQSGPELV KPGSSVKISCKAS GYSFTAYYMHW VKQSHGKSLEQI SGRINPDNGGNS YNQFKFGKAILT VDKSSNTAYMEL RSLTSEDSAVYY CAKSTSYDYDGY WFDVWGAGTTV TVSS	429	GYSF TAY Y	430	RINP D NGG	431	CAKS TSYD YDGY WFDV	432
CD221 (IGF1R)	SSELTQDPAVS VALGQTVRIT CQGDSLRSYY ATWYQQKPG QAPILVIYGEN KRPSGIPDRFS GSSSGNTASLT ITGAQAEDEA DYYCKSRDGS GQHLVFGGGT KLTVL	433	SLRS YY	434	GEN	435	KSRD GSG QHL V	436	EVQLVQSGAEVK KPGSSVKVSCKA SGGTFSSYAISW VRQAPGQGLEW MGGIIPIFGTANY AQKFQGRVTITA DKSTSTAYMELS SLRSEDTAVYYC ARAPLRFLEWST QDHYYYYYMDV WGKGTTVTVSS	437	GGTF SSYA	438	IIPI FGTA	439	ARAP LRFL EWST QDHY YYYY MDV	440

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
CD221 (IGF1R)	EIVLTQSPGTL SVSPGERATLS CRASQSIGSSL HWYQQKPGQ APRLLIKYASQ SLSGIPDRFSG SGSGTDFTLTI SRLEPEDFAV YYCHQSSRLP HTFGQGTKVE IK	441	QSIG SS	442	YAS	443	HQSS RLPH T	444	EVQLVQSGGGLV KPGGSLRLSCAA SGFTFSSFAMHW VRQAPGKGLEWI SVIDTRGATYYA DSVKGRFTISRD NAKNSLYLQMN SLRAEDTAVYYC ARLGNFYYGMD VWGQGTTVTVSS	445	GFTF SSFA	446	IDTR GAT	447	ARLG NFYY GMDV	448
CD221 (IGF1R)	EIVLTQSPATL SLSPGERATLS CRASQSVSSY LAWYQQKPG QAPRLLIYDAS KRATGIPARFS GSGSGTDFTLT ISSLEPEDFAV YYCQQRSKWP PWTFGQGTKV ESK	449	QSVS SY	450	DAS	451	QQRS KWP PWT	452	QVELVESGGGVV QPGRSQRLSCAA SGFTFSSYGMHW VRQAPGKGLEW VAIIWFDGSSTYY ADSVRGRFTISRD NSKNTLYLQMNS LRAEDTAVYFCA RELGRRYFDLWG RGTLVSVSS	453	GFTF SSYG	454	IWFD GSST	455	AREL GRRY FDL	456
CD221 (IGF1R)	DIVMTQSPLSL PVTPGEPASIS CRSSQSIVHSN GNTYLQWYL QKPGQSPQLLI YKVSNRLYGV PDRFSGSGSGT DFTLKISRVEA EDVGVYYCFQ GSHVPWTFGQ GTKVEIK	457	QSIV HSNG NTY	458	KVS	459	FQGS HVP WT	460	QVQLQESGPGLV KPSETLSLTCTVS GYSITGGYLWN WIRQPPGKGLEW IGYISYDGTNNY KPSLKDRVTISRD TSKNQFSLKLSSV TAADTAVYYCA RYGRVFFDYWG QGTLVTVSS	461	GYSI TGG YL	462	ISYD GTN	463	ARYG RVFF DY	464
CD221 (IGF1R)	DVVMTQSPLS LPVTPGEPASI SCRSSQSLLHS NGYNYLDWY LQKPGQSPQL LIYLGSNRASG VPDRFSGSGS GTDFTLKISRV EAEDVGVYYC MQGTHWPLTF GQGTKVEIK	465	QSLL HSNG YNY	466	LGS	467	MQG THW PLT	468	QVQLQESGPGLV KPSGTLSLTCAVS GGSISSSNWWSW VRQPPGKGLEWI GEIYHSGSTNYN PSLKSRVTISVDK SKNQFSLKLSSVT AADTAVYYCAR WTGRTDAFDIW GQGTMVTVSS	469	GGSI SSSN W	470	IYHS GST	471	ARWT GRTD AFDI	472

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
CD223 (L4G-3)	EIVLTQSPATL SLSPGERATLS CRASQSISSYL AWYQQKPGQ APRLLIYDASN RATGIPARFSG SGSGTDFTLTI SSLEPEDFAVY YCQQRSNWPL TFGQGTNLEIK	473	QSIS SY	474	DAS	475	QQRS NWP LT	476	QVQLQQWGAGL LKPSETLSLTCAV YGGSFSDYYWN WIRQPPGKGLEW IGEINHRGSTNSN PSLKSRVTLSLDT SKNQFSLKLRSV TAADTAVYYCAF GYSDYEYNWFD PWGQGTLVTVSS	477	GGSF SDY Y	478	INHR GST	479	AFGY SDYE YNWF DP	480
CD248	DIQMTQSPSSL SASVGDRVTIT CRASQNVGTA VAWLQQTPG KAPKLLIYSAS NRYTGVPSRF SGSGSGTDYT FTISSLQPE-DIA TYYCQQYTNY PMYTFGQGTK VQIK	481	QNVG TA	482	SAS	483	QQY TNYP MYT	484	QVQLQESGPGLV RPSQTLSLTCTAS GYTFTDYVIHWV KQPPGRGLEWIG YINPYDDDTTYN QKFKGRVTMLV DTSSNTAYLRLSS VTAEDTAVYYC ARRGNSYDGYFD YSMDYWGSGTP VTVSS	485	GYTF TDY V	486	INPY DDDT	487	ARRG NSYD GYFD YSMD Y	488
CD25	QIVSTQSPAIM SASPGEKVTM TCSASSSRSY MQWYQQKPG TSPKRWIYDTS KLASGVPARF SGSGSGTSYSL TISSMEAEDA ATYYCHQRSS YTFGGGTKLEI K	489	SSRS Y	490	DTS	491	HQRS SYT	492	QLQQSGTVLARP GASVKMSCKAS GYSFTRYWMHW IKQRPGQGLEWI GAIYPGNSDTSY NQKFEGKAKLTA VTSASTAYMELS SLTHEDSAVYYC SRDYGYYFDFW GQGTTLTVSS	493	GYSF TRY W	494	IYPG NSDT	495	SRDY GYYF DF	496
CD25	DIQMTQSPSTL SASVGDRVTIT CSASSSISYMH WYQQKPGKA PKLLIYTTSNL ASGVPARFSG SGSGTEFTLTI SSLQPDDFAT YYCHQRSTYP LTFGQGTKVE VK	497	SSIS Y	498	TTS	499	HQRS TYPL T	500	QVQLVQSGAEV KKPGSSVKVSCK ASGYTFTSYRMH WVRQAPGQGLE WIGYINPSTGYTE YNQKFKDKATIT ADESTNTAYMEL SSLRSEDTAVYY CARGGGVFDYW GQGTLVTVSS	501	GYTF TSYR	502	INPS TGYT	503	ARGG GVFD YW	504

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
CD252 (OX40L)	DIQMTQSPSSL SASVGDRVTIT CRASQDISNYL NWYQQKPGK APKLLIYYTSK LHSGVPSRFSG SGSGTDYTLTI SSLQPEDFATY YCQQGSALPW TFGQGTKVEI K	505	QDIS NY	506	YTS	507	QQG SALP WT	508	QVQLQESGPGLV KPSQTLSLTCAV YGGSFSSGYWN WIRKHPGKGLEY IGYISYNGITYHN PSLKSRITINRDTS KNQYSLQLNSVT PEDTAVYYCARY KYDYDGGHAMD YWGQGTLVTVSS	509	GGSF SSGY	510	ISYN GIT	511	ARYK YDYD GGHA MDY	512
CD254 (RANKL)	EIVLTQSPGTL SLSPGERATLS CRASQSVRGR YLAWYQQKP GQAPRLLIYG ASSRATGIPDR FSGSGSGTDFT LTISRLEPEDF AVFYCQQYGS SPRTFGQGTK VEIK	513	QSVR GRY	514	GAS	515	QQY GSSP RT	516	EVQLLESGGGLV QPGGSLRLSCAA SGFTFSSYAMSW VRQAPGKGLEW VSGITGSGGSTY YADSVKGRFTIS RDNSKNTLYLQ MNSLRAEDTAV YYCAKDPGTTVI MSWFDPWGQGT LVTVSS	517	GFTF SSYA	518	ITGS GGST	519	AKDP GTTV IMSW FDP	520
CD257 (BAFF)	EIVLTQSPATL SLSPGERATLS CRASQSVSRY LAWYQQKPG QAPRLLIYDAS NRATGIPARFS GSGSGTDSTLT ISSLEPEDFAV YYCQQRSNWP RTFGQGTKVEI K	521	QSVS RY	522	DAS	523	QQRS NWP RT	524	QVQLQQWGAGL LKPSETLSLTCAV YGGSFSGYYWS WIRQPPGKGLEW IGEINHSGSTNYN PSLKSRVTISVDT SKNQFSLKLSSVT AADTAVYYCAR GYYDILTGYYYY FDYWGQGTLVT VSS	525	GGSF SGY Y	526	INHS GST	527	ARGY YDIL TGYY YYFD Y	528
CD257 (BAFF)	SSELTQDPAVS VALGQTVRVT CQGDSLRSYY ASQYQQKPGQ APVLVIYGKN NRPSGIPDRFS GSSSGNTASLT ITGAQAEDEA DYYCSSRDSS GNHWVFGGG TEL	529	SLRS YY	530	GKN	531	SSRD SSGN HWV	532	QVQLQQSGAEV KKPGSSVRVSCK ASGGTFNNNAIN WVRQAPGQGLE WMGGIIPMFGTA KYSQNFQGRVAI TADESTGTASME LSSLRSEDTAVY YCARSRDLLLFP HHALSPWGRGT MVTVSS	533	GGTF NNN A	534	IIPM FGTA	535	ARSR DLLL FPHH ALSP	536

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
CD26	QIVLTQSPAIMSASPGEKVTITCSASSSVSYMNWFQQKPGTSPKLWIYSTSNLASGVPARFSGSGSGTSYSLTISRMEAEDAATYYCQQRSSYPNTFGGGTKLEIK	537	SSVSY	538	STS	539	QQRSSYPNT	540	QVQLQQSGAELVKPGASVKLSCKASGYTFRSYDINWVRQRPEQGLEWIGWIFPGDGSTKYNEKFKGKATLTTDKSSSTAYMQLSRLTSEDSAVYFCARWTVVGPGYFDVWGAGTTVTVSS	541	GYTFRSYD	542	IFPGDGST	543	ARWTVVGPGYFDV	544
CD262 (DR5)	DIQMTQSPSSLSASVGDRVTITCKASQDVGTAVAWYQQKPGKAPKLLIYWASTRHTGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYSSYRTFGQGTKVEIK	545	QDVGTA	546	WAS	547	QQYSSYRT	548	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYVMSWVRQAPGKGLEWVATISSGGSYTYYPDSVKGRFTISRDNAKNTLYLQMNSLRAEDTAVYYCARRGDSMITTDYWGQGTLVTVSS	549	GFTFSSYV	550	ISSGGSYT	551	ARRGDSMITTDYW	552
CD262 (DR5)	SSELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVIYGKNNRPSGIPDRFSGSSSGNTASLTITGAQAEDEADYYCNSRDSSGNHVVFGGGTKLTVL	553	SLRSYY	554	GKN	555	NSRDSSGNHVV	556	EVQLVQSGGGVERPGGSLRLSCAASGFTFDDYGMSWVRQAPGKGLEWVSGINWNGGSTGYADSVKGRVTISRDNAKNSLYLQMNSLRAEDTAVYYCAKILGAGRGWYFDLWGKGTTVTVSS	557	GFTFDDYG	558	INWNGGST	559	AKILGAGRGWYFDL	560
CD262 (DR5)	EIVLTQSPGTLSLSPGERATLSCRASQGISRSYLAWYQQKPGQAPSLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQFGSSPWTFGQGTKVEIK	561	QGISRSY	562	GAS	563	QQFGSSPWT	564	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGDYFWSWIRQLPGKGLEWIGHIHNSGTTYYNPSLKSRVTISVDTSKKQFSLRLSSVTAADTAVYYCARDRGGDYYYGMDVWGQGTTVTVSS	565	GGSISSGDYF	566	IHNSGTT	567	ARDRGGDYYYGMDV	568

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
CD27	DIQMTQSPSSL SASVGDRVTIT CRASQGISRW LAWYQQKPE KAPKSLIYAAS SLQSGVPSRFS GSGSGTDFTLT ISSLQPEDFAT YYCQQYNTYP RTFGQGTKVEI K	569	QGIS RW	570	AAS	571	QQY NTYP RT	572	QVQLVESGGGV VQPGRSLRLSCA ASGFTFSSYDMH WVRQAPGKGLE WVAVIWYDGSN KYYADSVKGRFT ISRDNSKNTLYL QMNSLRAEDTA VYYCARGSGNW GFFDYWGQGTL VTVSS	573	GFTF SSYD	574	IWYD GSNK	575	ARGSG NWGFF DY	576
CD274 (PD-L1)	QSALTQPASV SGSPGQSITISC TGTSSDVGGY NYVSWYQQH PGKAPKLMIY DVSNRPSGVS NRFSGSKSGN TASLTISGLQA EDEADYYCSS YTSSSTRVFGT GTKVTVL	577	SSDV GGYN Y	578	DVS	579	SSYT SSST RV	580	EVQLLESGGGLV QPGGSLRLSCAA SGFTFSSYIMMW VRQAPGKGLEW VSSIYPSGGITFY ADTVKGRFTISR DNSKNTLYLQM NSLRAEDTAVYY CARIKLGTVTTV DYWGQGTLVTV SS	581	GFTF SSYI	582	IYPS GGIT	583	ARIK LGTV TTVD Y	584
CD274 (PD-L1)	DIQMTQSPSSL SASVGDRVTIT CRASQDVSTA VAWYQQKPG KAPKLLIYSAS FLYSGVPSRFS GSGSGTDFTLT ISSLQPEDFAT YYCQQYLYHP ATFGQGTKVE IK	585	QDVST A	586	SAS	587	QQY LYHP AT	588	EVQLVESGGGLV QPGGSLRLSCAA SGFTFSDSWIHW VRQAPGKGLEW VAWISPYGGSTY YADSVKGRFTIS ADTSKNTAYLQ MNSLRAEDTAV YYCARRHWPGG FDYWGQGTLVT VSS	589	GFTF SDS W	590	ISPY GGST	591	ARRH WPGG FDY	592
CD274 (PD-L1)	EIVLTQSPGTL SLSPGERATLS CRASQRVSSS YLAWYQQKP GQAPRLLIYD ASSRATGIPDR FSGSGSGTDFT LTISRLEPEDF AVYYCQQYGS LPWTFGQGTK VEIK	593	QRVS SSY	594	DAS	595	QQY GSLP WT	596	EVQLVESGGGLV QPGGSLRLSCAA SGFTFSRYWMS WVRQAPGKGLE WVANIKQDGSEK YYVDSVKGRFTI SRDNAKNSLYLQ MNSLRAEDTAV YYCAREGGWFG ELAFDYWGQGT LVTVSS	597	GFTF SRY W	598	IKQD GSEK	599	AREG GWFG ELAF DY	600

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
CD275 (ICOS-L)	DIQMTQSPSSL SASVGDRVTIT CRASQGISNW LAWYQQKPE KAPKSLIYAAS SLQSGVPSRFS GSGSGTDFTLT ISSLQPEDFAT YYCQQYDSYP RTFGQGTKVEI K	601	QGIS NW	602	AAS	603	QQY DSYP RT	604	EVQLVESGGGLV QPGGSLRLSCAA SGFTFSSYWMSW VRQAPGKGLEW VAYIKQDGNEKY YVDSVKGRFTIS RDNAKNSLYLQ MNSLRAEDTAV YYCAREGILWFG DLPTFWGQGTLV TVSS	605	GFTF SSY W	606	IKQD GNEK	607	AREG ILWF GDLP TF	608
CD276 (B7H3)	DIQLTQSPSFL SASVGDRVTIT CKASQNVDTN VAWYQQKPG KAPKALIYSAS YRYSGVPSRFS GSGSGTDFTLT ISSLQPEDFAT YYCQQYNNYP FTFGQGTKLEI K	609	QNVD TN	610	SAS	611	QQY NNY PFT	612	EVQLVESGGGLV QPGGSLRLSCAA SGFTFSSFGMHW VRQAPGKGLEW VAYISSDSSAIYY ADTVKGRFTISR DNAKNSLYLQM NSLRDEDTAVYY CGRGRENIYYGS RLDYWGQGTTV TVSS	613	GFTF SSFG	614	ISSD SSAI	615	GRGR ENIY YGSR LDY	616
CD276 (B7H3)	DIVMTQSPAT LSVTPGDRVS LSCRASQSISD YLHWYQQKS HESPRLLIKYA SQSIS-GIPSRFS GSGSGSDFTLS INSVEPEDVGV YYCQNGHSFP LTFGAGTKLE LK	617	QSIS DY	618	YAS	619	QNG HSFP LT	620	QVQLQQSGAELV KPGASVKLSCKA SGYTFTNYDINW VRQRPEQGLEWI GWIFPGDGSTQY NEKFKGKATLTT DTSSSTAYMQLS RLTSEDSAVYFC ARQTTATWFAY WGQGTLVTVSA	621	GYTF TNY D	622	IFPG DGST	623	ARQT TATW FAY	624
CD279 (PD-1)	DIQMTQSPSSL SASVGDSITIT CRASLSINTFL NWYQQKPGK APNLLIYAASS LHGGVPSRFS GSGSGTDFTLT IRTLQPEDFAT YYCQQSSNTP FTFGPGTVVD FR	625	LSIN TF	626	AAS	627	QQSS NTPF T	628	EVQLLESGGVLV QPGGSLRLSCAA SGFTFSNFGMTW VRQAPGKGLEW VSGISGGGRDTY FADSVKGRFTISR DNSKNTLYLQM NSLKGEDTAVYY CVKWGNIYFDY WGQGTLVTVSS	629	GFTF GSNF G	630	ISGG RDT DY	631	VKWG NIYF	632

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
CD279 (PD-1)	DIQMTQSPSSL SASVGDRVTIT CLASQTIGTW LTWYQQKPG KAPKLLIYTAT SLADGVPSRFS GSGSGTDFTLT ISSLQPEDFAT YYCQQVYSIP WTFGGGTKVE IK	633	QTIG TW	634	TAT	635	QQV YSIP WT	636	EVQLVESGGGLV QPGGSLRLSCAA SGFTFSSYMMSW VRQAPGKGLEW VATISGGGANTY YPDSVKGRFTISR DNAKNSLYLQM NSLRAEDTAVYY CARQLYYFDYW GQGTTVTVSS	637	GFTF SSY M	638	ISGG GANT	639	ARQL YYFD Y	640
CD279 (PD-1)	EIVLTQSPATL SLSPGERATLS CRASQSVSSY LAWYQQKPG QAPRLLIYDAS NRATGIPARFS GSGSGTDFTLT ISSLEPEDFAV YYCQQSSNWP RTFGQGTKVEI K	641	QSVS SY	642	DAS	643	QQSS NWP RT	644	QVQLVESGGGV VQPGRSLRLDCK ASGITFSNSGMH WVRQAPGKGLE WVAVIWYDGSK RYYADSVKGRFT ISRDNSKNTLFLQ MNSLRAEDTAV YYCATNDDYWG QGTLVTVSS	645	GITF SNSG	646	IWYD GSKR	647	ATND DY	648
CD279 (PD-1)	DIQMTQSPSSV SASVGDRVTIT CRASQGISSW LAWYQQKPG KAPKLLISAAS SLQSGVPSRFS GSGSGTDFTLT ISSLQPEDFAT YYCQQANHLP FTFGGGTKVEI K	649	QGIS SW	650	AAS	651	QQA NHLP FT	652	QVQLVQSGAEV KKPGSSVKVSCK ASGGTFSSYAIS WVRQAPGQGLE WMGLIIPMFDTA GYAQKFQGRVAI TVDESTSTAYME LSSLRSEDTAVY YCARAEHSSTGT FDYWGQGTLVT VSS	653	GGTF SSYA	654	IIPM FDTA	655	ARAE HSST GTFD Y	656
CD279 (PD-1)	QPVLTQPLSVS VALGQTARIT CGGNNIGSKN VHWYQQKPG QAPVLVIYRD SNRPSGIPERF SGSNSGNTAT LTISRAQAGDE ADYYCQVWD SSTAVFGTGT KLTVL	657	NIGS KN	658	RDS	659	QVW DSST AV	660	QVQLVQSGGGL VQPGGSLRLSCA ASGFTFSSYWMY WVRQVPGKGLE WVSAIDTGGGRT YYADSVKGRFAI SRVNAKNTMYL QMNSLRAEDTA VYYCARDEGGG TGWGVLKDWPY GLDAWGQGTLV TVSS	661	GFTF SSY W	662	IDTG GGRT	663	ARDE GGGT GWGV LKDW PYGL DA	664

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
CD279 (PD-1)	EIVLTQSPATL SLSPGERATLS CRASKGVSTS GYSYLHWYQ QKPGQAPRLLI YLASYLESGV PARFSGSGSGT DFTLTISSLEPE DFAVYYCQHS RDLPLTFGGG TKVEIK	665	KGVS TSGY SY	666	LAS	667	QHSR DLPL T	668	QVQLVQSGVEV KKPGASVKVSCK ASGYTFTNYYM YWVRQAPGQGL EWMGGINPSNGG TNFNEKFKNRVT LTTDSSTTTAYM ELKSLQFDDTAV YYCARRDYRFD MGFDYWGQGTT VTVSS	669	GYTF TNY Y	670	INPS NGGT	671	ARRD YRFD MGFD YW	672
CD279 (PD-1)	EIVLTQSPATL SLSPGERATLS CRASQSVRSY LAWYQQKPG QAPRLLIYDAS NRATGIPARFS GSGSGTDFTLT ISSLEPEDFAV YYCQQRNYW PLTFGQGTKV EIK	673	QSVR SY	674	DAS	675	QQR NYW PLT	676	VQLVQSGAEVK KPGSSVKVSCKA SGGTFSSYAISW VRQAPGQGLEW MGGIIPIFDTANY AQKFQGRVTITA DESTSTAYMELS SLRSEDTAVYYC ARPGLAAAYDTG SLDYWGQGTLV TVSS	677	GGTF SSYA	678	IIPI FDTA	679	ARPG LAAA YDTG SLDY	680
CD3	DIQLTQSPAIM SASPGEKVTM TCRASSSVSY MNWYQQKSG TSPKRWIYDTS KVASGVPYRF SGSGSGTSYSL TISSMEAEDA ATYYCQQWSS NPLTFGAGTK LELK	681	SSVS Y	682	DTS	683	QQW SSNP LT	684	DIKLQQSGAELA RPGASVKMSCKT SGYTFTRYTMH WVKQRPGQGLE WIGYINPSRGYT NYNQKFKDKAT LTTDKSSSTAYM QLSSLTSEDSAV YYCARYYDDHY CLDYWGQGTTL TVSS	685	GYTF TRYT	686	INPS RGYT	687	ARYY DDHY CLDY	688
CD3	DIQLTQPNSVS TSLGSTVKLSC TLSSGNIENNY VHWYQLYEG RSPTTMIYDD DKRPDGVPDR FSGSIDRSSNS AFLTIHNVAIE DEAIYFCHSY VSSFNVFGGG TKLTVL	689	SGNI ENNY	690	DDD	691	HSY VSSF NV	692	EVQLLESGGGLV QPGGSLRLSCAA SGFTFSSFPMAW VRQAPGKGLEW VSTISTSGGRTYY RDSVKGRFTISRD NSKNTLYLQMNS LRAEDTAVYYCA KFRQYSGGFDY WGQGTLVTVSS	693	GFTF SSFP	694	ISTS GGRT	695	AKFR QYSG GFDY	696

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
CD3	DIQMTQTTSSL SASLGDRVTIS CRASQDIRNY LNWYQQKPD GTVKLLIYYTS RLHSGVPSKFS GSGSGTDYSL TISNLEQEDIA TYFCQQGNTL PWTFAGGTKL EIK	697	QDIR NY	698	YTS	699	QQG NTLP WTF AGG	700	EVQLQQSGPELV KPGASMKISCKA SGYSFTGYTMN WVKQSHGKNLE WMGLINPYKGVS TYNQKFKDKATL TVDKSSSTAYME LLSLTSEDSAVY YCARSGYYGDSD WYFDVWGQGTT LTVFS	701	GYSF TGY T	702	INPY KGVS	703	ARSG YYGD SDWY FDV	704
CD3	QTVVTQEPSL TVSPGGTVTL TCGSSTGAVT SGNYPNWVQ QKPGQAPRGL IGGTKFLAPGT PARFSGSLLGG KAALTLSGVQ PEDEAEYYCV LWYSNRWVF GGGTKLTVL	705	TGAVT SGNY	706	GTK	707	VLW YSNR WV	708	EVQLVESGGGLV QPGGSLKLSCAA SGFTFNKYAMN WVRQAPGKGLE WVARIRSKYNNY ATYYADSVKDRF TISRDDSKNTAY LQMNNLKTEDT AVYYCVRHGNF GNSYISYWAYW GQGTLVTVSS	709	GFTF NKY A	710	IRSK YNNY AT	711	VRHG NFGN SYIS YWAY	712
CD3	DFVMTQSPDS LAVSLGERVT MSCKSSQSLL NSGNQKNYLT WYQQKPGQPP KLLIYWASTR ESGVPDRFSGS GSGTDFTLTIS SLQAEDVAVY YCQNDYSYPY TFGQGTKLEIK	713	QSLL NSGN QKNY	714	WAS	715	QND YSYP YT	716	EVQLVQSGAELK KPGASVKVSCKA SGYTFTDYYMK WVRQAPGQGLE WIGDIIPSNGATF YNQKFKGRVTIT VDKSTSTAYMEL SSLRSEDTAVYY CARSHLLRASWF AYWGQGTLVTV SS	717	GYTF TDY Y	718	IIPS NGAT	719	ARSH LLRA SWFA YW	720
CD3	QIVLTQSPAIM SASPGEKVTM TCSASSSVSY MNWYQQKSG TSPKRWIYDTS KLASGVPAHF RGSGSGTSYSL TISGMEAEDA ATYYCQQWSS NPFTFGSGTKL EIN	721	SSVS Y	722	DTS	723	QQW SSNP FT	724	QVQLQQSGAELA RPGASVKMSCKA SGYTFTRYTMH WVKQRPGQGLE WIGYINPSRGYT NYNQKFKDKAT LTTDKSSSTAYM QLSSLTSEDSAV YYCARYYDDHY CLDYWGQGTTL TVSS	725	GYTF TRYT	726	INPS RGYT	727	ARYY DDHY CLDY	728

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
CD3	EIVLTQSPATL SLSPGERATLS CRASQSVSSY LAWYQQKPG QAPRLLIYDAS NRATGIPARFS GSGSGTDFTLT ISSLEPEDFAV YYCQQRSNWP PLTFGGGTKV EIK	729	QSVS SY	730	DAS	731	QQRS NWP PLT	732	QVQLVESGGGV VQPGRSLRLSCA ASGFKFSGYGMH WVRQAPGKGLE WVAVIWYDGSK KYYVDSVKGRFT ISRDNSKNTLYL QMNSLRAEDTA VYYCARQMGYW HFDLWGRGTLVT VSS	733	GFKF SGY G	734	IWYD GSKK	735	ARQM GYWH FDL	736
CD3	DIQMTQSPSSL SASVGDRVTIT CRASQSISSYL NWYQQKPGK APKLLIYAASS LQSGVPSRFSG SGSGTDFTLTI SSLQPEDFATY YCQQSYSTPPT FGQGTKVEIK	737	QSIS SY	738	AAS	739	QQS YSTP PT	740	QVQLVQSGAEV KKPGASVKVSCK ASGYTFTSYYMH WVRQAPGQGLE WMGIINPSGGSTS YAQKFQGRVTM TRDTSTSTVYME LSSLRSEDTAVY YCAKGTTGDWF DYWGQGTLVTV SS	741	GYTF TSYY	742	INPS GGST	743	AKGT TGDW FDY	744
CD30 (TNFRS F8)	DIVLTQSPASL AVSLGQRATIS CKASQSVDFD GDSYMNWYQ QKPGQPPKVLI YAASNLESGIP ARFSGSGSGT DFTLNIHPVEE EDAATYYCQQ SNEDPWTFGG GTKLEIK	745	QSVD FDGD SY	746	AAS	747	QQS NEDP WT	748	QIQLQQSGPEVV KPGASVKISCKA SGYTFTDYYITW VKQKPGQGLEWI GWIYPGSGNTKY NEKFKGKATLTV DTSSSTAFMQLSS LTSEDTAVYFCA NYGNYWFAYWG QGTQVTVSA	749	GYTF TDY Y	750	IYPG SGNT	751	ANYG NYWF AY	752
CD30 (TNFRS F8)	DIQMTQSPTSL SASVGDRVTIT CRASQGISSW LTWYQQKPEK APKSLIYAASS LQSGVPSRFSG SGSGTDFTLTI SSLQPEDFATY YCQQYDSYPI TFGQGTRLEIK	753	QGIS SW	754	AAS	755	QQY DSYP IT	756	QVQLQQWGAGL LKPSETLSLTCAV YGGSFSAYYWS WIRQPPGKGLEW IGDINHGGGTNY NPSLKSRVTISVD TSKNQFSLKLNS VTAADTAVYYC ASLTAYWGQGSL VTVSS	757	GGSF SAY Y	758	INHG GGT	759	ASLT AY	760

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
CD319 (SLAMF 7)	DIQMTQSPSSL SASVGDRVTIT CKASQDVGIA VAWYQQKPG KVPKLLIYWA STRHTGVPDR FSGSGSGTDFT LTISSLQPEDV ATYYCQQYSS YPYTFGQGTK VEIK	761	QDVG IA	762	WAS	763	QQY SSYP YT	764	EVQLVESGGGLV QPGGSLRLSCAA SGFDFSRYWMS WVRQAPGKGLE WIGEINPDSSTIN YAPSLKDKFIISR DNAKNSLYLQM NSLRAEDTAVYY CARPDGNYWYF DVWGQGTLVTV SS	765	GFDF SRY W	766	INPD SSTI	767	ARPD GNYW YFDV	768
CD33	DIVLTQSPTIM SASPGERVTM TCTASSSVNYI HWYQQKSGD SPLRWIFDTSK VASGVPARFS GSGSGTSYSLT ISTMEAEDAA TYYCQQWRS YPLTFGDGTR LELK	769	SSVN Y	770	DTS	771	QQW RSYP LT	772	EVKLQESGPELV KPGASVKMSCK ASGYKFTDYVVH WLKQKPGQGLE WIGYINPYNDGT KYNEKFKGKATL TSDKSSSTAYME VSSLTSEDSAVY YCARDYRYEVY GMDYWGQGTSV TVSS	773	GYK FTDY V	774	INPY NDGT	775	ARDY RYEV YGMD Y	776
CD33	DIVMTQSPSSL SASLGGKVTIT CKASQDINKYI AWYQHKPGK GPRLLIHYTST LQPGIPSRFSG SGSGRDYSFSI SNLEPEDIATY YCLQYDNLLT FGAGTKLELK	777	QDIN KY	778	YTS	779	LQY DNLL T	780	EVKLQQSGPELV KPGTSVKVSCKA SGYSFTDYNMY WVKQSHGKSLE WIGYIDPYKGGTI YNQKFKGKATLT VDKSSSTAFMHL NSLTSEDSAVYY CAREMITAYYFD YWGQGSSVTVSS	781	GYSF TDY N	782	IDPY KGGT	783	AREM ITAY YFDY	784
CD33	DIVLTQSPASL AVSLGQRATIS CRASESVDNY GISFMNWFQQ KPGQPPKLLIY AASNQGSGVP ARFSGSGSGT DFSLNIHPMEE DDTAMYFCQ QSKEVPWTFG GGTKLEIK	785	ESVD NYGI SF	786	AAS	787	QQS KEVP WT	788	EVQLQQSGPELV KPGASVKISCKA SGYTFTDYNMH WVKQSHGKSLE WIGYIYPYNGGT GYNQKFKSKATL TVDNSSSTAYMD VRSLTSEDSAVY YCARGRPAMDY WGQGTSVTVSS	789	GYTF TDY N	790	IYPY NGGT	791	ARGR PAMD Y	792

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
CD33	DIQLTQSPSTL SASVGDRVTIT CRASESLDNY GIRFLTWFQQ KPGKAPKLLM YAASNQGSGV PSRFSGSGSGT EFTLTISSLQP DDFATYYCQQ TKEVPWSFGQ GTKVEVK	793	ESLD NYGI RF	794	AAS	795	QQT KEVP WS	796	EVQLVQSGAEVK KPGSSVKVSCKA SGYTITDSNIHW VRQAPGQSLEWI GYIYPYNGGTDY NQKFKNRATLTV DNPTNTAYMELS SLRSEDTAFYYC VNGNPWLAYWG QGTLVTVSS	797	GYTI TDSN	798	IYPYN GGT	799	VNGNP WLAY	800
CD33	NIMLTQSPSSL AVSAGEKVTM SCKSSQSVFFS SSQKNYLAWY QQIPGQSPKLL IYWASTRESG VPDRFTGSGS GTDFTLTISSV QSEDLAIYYC HQYLSSRTFG GGTKLEIK	801	QSVF FSSS QKNY	802	WAS	803	HQY LSSR T	804	QVQLQQPGAEV VKPGASVKMSC KASGYTFTSYYI HWIKQTPGQGLE WVGVIYPGNDDI SYNQKFKGKATL TADKSSTTAYMQ LSSLTSEDSAVY YCAREVRLRYFD VWGAGTTVTVSS	805	GYTF TSYY	806	IYPG NDDI	807	AREV RLRY FDV	808
CD33	DIKMTQSPSS MYASLGERVII NCKASQDINS YLSWFQQKPG KSPKTLIYRAN RLVDGVPSRF SGSGSGQDYS LTISSLEYEDM GIYYCLQYDE FPLTFGAGTKL ELK	809	QDIN SY	810	RAN	811	LQY DEFP LT	812	QVQLQQSGPELV RPGTFVKISCKAS GYTFTNYDINWV NQRPGQGLEWIG WIYPGDGSTKYN EKFKAKATLTAD KSSSTAYLQLNN LTSENSAVYFCA SGYEDAMDYWG QGTSVTVSS	813	GYTF TNY D	814	IYPG DGST	815	ASGY EDAM DY	816
CD33	DIQMTQSPSSL SASVGDRVTIT CRASESVDNY GISFMNWFQQ KPGKAPKLLL YAASNQGSGV PSRFSGSGSGT DFTLTISSLQP DDFATYYCQQ SKEVPWTFGQ GTKVELK	817	ESVD NYGI SF	818	AAS	819	QQS KEVP WT	820	QVQLVQSGAEV KKPGSSVKVSCK ASGYTFTDYNM HWVRQAPGQGL EWLGYIYPYNGG TGYNQKFKSKAT ITADESTNTAYM ELSSLRSEDTAV YYCARGRPAMD YWGQGTLVTVSS	821	GYTF TDY N	822	IYPY NGGT	823	ARGR PAMD YW	824

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
CD332 (FGFR2)	QSVLTQPPSAS GTPGQRVTISC SGSSSNIGNNY VSWYQQLPGT APKLLIYENY NRPAGVPDRF SGSKSGTSASL AISGLRSEDEA DYYCSSWDDS LNYWVFGGG TKLTVL	825	SSNI GNNY	826	ENY N	827	SSW DDSL NYW V	828	EVQLLESGGGLV QPGGSLRLSCAA SGFTFSSYAMSW VRQAPGKGLEW VSAISGSGTSTYY ADSVKGRFTISR DNSKNTLYLQM NSLRAEDTAVYY CARVRYNWNHG DWFDPWGQGTL VTVSS	829	GFTF SSYA	830	ISGS GTST	831	ARVR YNWN HGDW FDP	832
CD350 (FZD 10)	DIQMTQSPASL SVSVGETVTIT CRASENIYSNL AWYQQKQGK SPQLLVYVAT NLADGVPSRF SGSGSGTQYS LKINSLQSEDF GSYYCQHFW GTPYTFGGGT KLEIK	833	ENIY SN	834	VAT	835	QHF WGT PYT	836	EVQLQQSGAELV KPGASVKLSCTA SGFNINDTYMHW VKQRPEQGLEWI GRIDPANGNTKY DPKFQGKATITA DTSSNTAYLQLS SLTSEDTAVYYC ARGARGSRFAY WGQGTLVTVSA	837	GFNI NDT Y	838	IDPA NGNT	839	ARGA RGSR FAY	840
CD37	DIQMTQSPSSL SVSVGERVTIT CRASENIRSNL AWYQQKPGK SPKLLVNVAT NLADGVPSRF SGSGSGTDYS LKINSLQPEDF GTYYCQHYW GTTWTFGQGT KLEIK	841	ENIR SN	842	VAT	843	QHY WGT TWT	844	QVQVQESGPGLV APSQTLSITCTVS GFSLTTSGVSWV RQPPGKGLEWLG VIWGDGSTNYHP SLKSRLSIKKDHS KSQVFLKLNSLT AADTATYYCAK GGYSLAHWGQG TLVTVSS	845	GFSL TTSG	846	IWGD GST	847	AKGG YSLA H	848
CD371 (CLEC12A)	DIQMTQSPSSL SASVGDRVTIT CRASQSISSYL NWYQQKPGK APKLLIYAASS LQSGVPSRFSG SGSGTDFTLTI SSLQPEDFATY YCQQSYSTPPT FGQGTKVEIK	849	QSIS SY	850	AAS	851	QQS YSTP PT	852	QVQLVQSGGGV VQPGRSLRLSCV ASGFTFSSYGMH WVRQAPGKGLE WVAAIWYNARK QDYADSVKGRFT ISRDNSKNTLYL QMNSLRAEDTA VYYCTRGTGYN WFDPWGQGTLV TVSS	853	GFTF SSYG	854	IWYN ARKQ	855	TRGT GYNW FDP	856

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
CD38	DIVMAQSHKF MSTSVGDRVS ITCKASQDVST VVAWYQQKP GQSPKRLITSA SYRYIGVPDRF TGSGSGTDFTF TISSVQAEDLA VTTCQQHYSP YTFGGGTKLEI K	857	ASQD VS	858	ITSA	859	TCQ QHY SPYT	860	QVKLVESGGGLV KPGGSLKLSCEA SGFTFSSYTLSW VRQTPETRLEWV ATISIGGRYTTTP DSVEGRFTISRDN AKNTLYLQMNSL KSEDTAMYYCTR DFNGTSDFWGQ GTTLTVSS	861	GFTF SSYT	862	ISIG GRYT	863	TRDF NGTS DF	864
CD38	EIVLTQSPATL SLSPGERATLS CRASQSVSSY LAWYQQKPG QAPRLLIYDAS NRATGIPARFS GSGSGTDFTLT ISSLEPEDFAV YYCQQRSNWP PTFGQGTKVEI K	865	QSVS SY	866	DAS	867	QQRS NWP PT	868	EVQLLESGGGLV QPGGSLRLSCAV SGFTFNSFAMSW VRQAPGKGLEW VSAISGSGGGTY YADSVKGRFTIS RDNSKNTLYLQ MNSLRAEDTAV YFCAKDKILWFG EPVFDYWGQGTL VTVSS	869	GFTF NSFA	870	ISGS GGGT	871	AKDK ILWF GEPV FDY	872
CD38	DIVMTQSHLS MSTSLGDPVSI TCKASQDVST VVAWYQQKP GQSPRRLIYSA SYRYIGVPDRF TGSGAGTDFT FTISSVQAEDL AVYYCQQHYS PPYTFGGGTK LEIK	873	QDVS TV	874	SAS	875	QQH YSPP YT	876	QVQLVQSGAEV AKPGTSVKLSCK ASGYTFTDYWM QWVKQRPGQGL EWIGTIYPGDGD TGYAQKFQGKA TLTADKSSKTVY MHLSSLASEDSA VYYCARGDYYG SNSLDYWGQGTS VTVSS	877	GYTF TDY W	878	IYPG GDT	879	ARGDY DYGS NSLD Y	880
CD4	DIVMTQSPDSL AVSLGERATIN CRASKSVSTS GYSYIYWYQQ KPGQPPKLLIY LASILESGVPD RFSGSGSGTDF TLTISSLQAED VAVYYCQHSR ELPWTFGQGT KVEIK	881	KSVS TSGY SY	882	LAS	883	QHSR ELP WT	884	EEQLVESGGGLV KPGGSLRLSCAA SGFSFSDCRMYW LRQAPGKGLEWI GVISVKSENYGA NYAESVRGRFTIS RDDSKNTVYLQ MNSLKTEDTAVY YCSASYYRYDVG AWFAYWGQGTL VTVSS	885	GFSF SDCR	886	ISVK SENY GA	887	SASY YRYD VGAW FAYW	888

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
CD4	DIVMTQSPDSL AVSLGERVTM NCKSSQSLLYS TNQKNYLAW YQQKPGQSPK LLIYWASTRES GVPDRFSGSG SGTDFTLTISS VQAEDVAVY YCQQYYSYRT FGGGTKLEIK	889	QSLL YSTN QKNY	890	WAS	891	QQY YSYR T	892	QVQLQQSGPEVV KPGASVKMSCK ASGYTFTSYVIH WVRQKPGQGLD WIGYINPYNDGT DYDEKFKGKATL TSDTSTSTAYME LSSLRSEDTAVY YCAREKDNYAT GAWFAYWGQGT LVTVSS	893	GYTF TSYV	894	INPY NDGT	895	AREK DNYA TGAW FAY	896
CD40	DIQMTQSPSSL SASVGDRVTIT CRSSQSLVHS NGNTFLHWY QQKPGKAPKL LIYTVSNRFSG VPSRFSGSGSG TDFTLTISSLQ PEDFATYFCSQ TTHVPWTFGQ GTKVEIK	897	QSLV HSNG NTF	898	TVS	899	SQTT HVP WT	900	EVQLVESGGGLV QPGGSLRLSCAA SGYSFTGYYIHW VRQAPGKGLEW VARVIPNAGGTS YNQKFKGRFTLS VDNSKNTAYLQ MNSLRAEDTAV YYCAREGIYWW GQGTLVTVSS	901	GYSF TGY Y	902	VIPN AGGT	903	AREG IYW	904
CD40	AIQLTQSPSSL SASVGDRVTIT CRASQGISSAL AWYQQKPGK APKLLIYDASN LESGVPSRFSG SGSGTDFTLTI SSLQPEDFATY YCQQFNSYPT FGQGTKVEIK	905	QGIS SA	906	DAS	907	QQF NSYP T	908	QLQLQESGPGLL KPSETLSLTCTVS GGSISSPGYYGG WIRQPPGKGLEW IGSIYKSGSTYHN PSLKSRVTISVDT SKNQFSLKLSSVT AADTAVYYCTRP VVRYFGWFDPW GQGTLVTVSS	909	GGSI SSPG YY	910	IYKS GST	911	TRPV VRYF GWFD P	912
CD40	DIVMTQSPLSL TVTPGEPASIS CRSSQSLLYSN GYNYLDWYL QKPGQSPQVLI SLGSNRASGV PDRFSGSGSGT DFTLKISRVEA EDVGVYYCM QARQTPFTFGP GTKVDIR	913	QSLL YSNG YNY	914	LGS	915	MQA RQTP FT	916	QVQLVESGGGV VQPGRSLRLSCA ASGFTFSSYGMH WVRQAPGKGLE WVAVISYEESNR YHADSVKGRFTI SRDNSKITLYLQ MNSLRTEDTAVY YCARDGGIAAPG PDYWGQGTLVT VSS	917	GFTF SSYG	918	ISYE ESNR	919	ARDG GIAA PGPD Y	920

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
CD40	DIQMTQSPSSV SASVGDRVTIT CRASQGIYSW LAWYQQKPG KAPNLLIYTAS TLQSGVPSRFS GSGSGTDFTLT ISSLQPEDFAT YYCQQANIFP LTFGGGTKVEI K	921	QGIY SW	922	TAS	923	QQA NIFP LT	924	QVQLVQSGAEV KKPGASVKVSCK ASGYTFTGYYM HWVRQAPGQGL EWMGWINPDSG GTNYAQKFQGR VTMTRDTSISTA YMELNRLRSDDT AVYYCARDQPL GYCTNGVCSYFD YWGQGTLVTVSS	925	GYTF TGY Y	926	INPD SGGT	927	ARDQ PLGY CTNG VCSY FDY	928
CD40L	DIQMTQSPSSL SASVGDRVTIT CRASEDLYYN LAWYQRKPG KAPKLLIYDT YRLADGVPSR FSGSGSGTDY TLTISSLQPED FASYYCQQYY KFPFTFGQGT KVEIK	929	EDLY YN	930	DTY	931	QQY YKFP FT	932	EVQLVESGGGLV QPGGSLRLSCAV SGFSSTNYHVHW VRQAPGKGLEW MGVIWGDGDTS YNSVLKSRFTISR DTSKNTVYLQM NSLRAEDTAVYY CARQLTHYYVLA AWGQGTLVTVSS	933	GFSS TNY H	934	IWGD GDT	935	ARQL THYY VLAA	936
CD40L	DIVLTQSPATL SVSPGERATIS CRASQRVSSST YSYMHWYQQ KPGQPPKLLIK YASNLESGVP ARFSGSGSGT DFTLTISSVEP EDFATYYCQH SWEIPPTFGGG TKLEIK DFVMTQSPAF	937	QRVS SSTY SY	938	YAS	939	QHS WEIP PT	940	QVQLVQSGAEV VKPGASVKLSCK ASGYIFTSYYMY WVKQAPGQGLE WIGEINPSNGDT NFNEKFKSKATL TVDKSASTAYME LSSLRSEDTAVY YCTRSDGRNDM DSWGQGTLVTVS S	941	GYIF TSYY	942	INPS NGDT	943	TRSD GRND MDS	944
CD49b (a2)	LSVTPGEKVTI TCSAQSSVNYI HWYQQKPDQ APKKLIYDTSK LASGVPSRFSG SGSGTDYTFTI SSLEAEDAAT YYCQQWTTNP LTFGQGTKVEI K	945	SSVN Y	946	DTS	947	QQW TTNP LT	948	QVQLQESGPGLV KPSETLSLTCTVS GFSLTNYGIHWIR QPPGKGLEWLGV IWARGFTNYNSA LMSRLTISKDNS KNQVSLKLSSVT AADTAVYYCAR ANDGVYYAMDY WGQGTLVTVSS	949	GFSL TNY G	950	IWAR GFT	951	ARAN DGVY YAMD Y	952

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
CD51 (a5)	DIQMTQSPSSL SASVGDRVTIT CRASQDISNYL AWYQQKPGK APKLLIYYTSK IHSGVPSRFSG SGSGTDYTFTI SSLQPEDIATY YCQQGNTFPY TFGQGTKVEI K	953	QDIS NY	954	YTS	955	QQG NTFP YT	956	QVQLQQSGGELA KPGASVKVSCKA SGYTFSSFWMH WVRQAPGQGLE WIGYINPRSGYTE YNEIFRDKATMT TDTSTSTAYMEL SSLRSEDTAVYY CASFLGRGAMD YWGQGTTVTVSS	957	GYTF SSFW	958	INPRS GYT	959	ASFL GRGA MDY	960
CD52	DIQMTQSPSSL SASVGDRVTIT CKASQNIDKY LNWYQQKPG KAPKLLIYNT NNLQTGVPSR FSGSGSGTDFT FTISSLQPE-DIA TYYCLQHISRP RTFGQGTKVEI K	961	QNID KY	962	NTN	963	LQHI SRPR T	964	QVQLQESGPGLV RPSQTLSLTCTVS GFTFTDFYMNW VRQPPGRGLEWI GFIRDKAKGYTT EYNPSVKGRVTM LVDTSKNQFSLR LSSVTAADTAVY YCAREGHTAAPF DYWGQGSLVTV SS	965	GFTF TDFY	966	IRDK AKGY TT	967	AREG HTAA PFDY	968
CD54(ICAM-1)	QSVLTQPPSAS GTPGQRVTISC TGSSSNIGAGY DVHWYQQLP GTAPKLLIYD NNNRPSGVPD RFSGSKSGTSA SLAISGLRSED EADYYCQSYD SSLSAWLFGG GTKLTVL	969	SSNI GAGY D	970	DNN	971	QSY DSSL SAW L	972	EVQLLESGGGLV QPGGSLRLSCAA SGFTFSNAWMS WVRQAPGKGLE WVAFIWYDGSN KYYADSVKGRFT ISRDNSKNTLYL QMNSLRAEDTA VYYCARYSGWY FDYWGQGTLVT VSS	973	GFTF SNA W	974	IWYD GSNK	975	ARYS GWYF Y	976
CD56	DVVMTQSPLS LPVTLGQPASI SCRSSQIIIHSD GNTYLEWFQQ RPGQSPRRLIY KVSNRFSGVP DRFSGSGSGT DFTLKISRVEA EDVGVYYCFQ GSHVPHTFGQ GTKVEIK	977	QIII HSDG NTY	978	KVS	979	FQGS HVP HT	980	QVQLVESGGGV VQPGRSLRLSCA ASGFTFSSFGMH WVRQAPGKGLE WVAYISSGSFTIY YADSVKGRFTIS RDNSKNTLYLQ MNSLRAEDTAV YYCARMRKGYA MDYWGQGTLVT VSS	981	GFTF SSFG	982	ISSG SFTI	983	ARMR KGYA MDY	984

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
CD61 (a4b3)	EIVLTQSPATL SLSPGERATLS CQASQSISNFL HWYQQRPGQ APRLLIRYRSQ SISGI- PARFSGS GSGTDFTLTIS SLEPEDFAVY YCQQSGSWPL TFGGGTKVEI K	985	QSIS NF	986	YRS	987	QQS GSW PLT	988	QVQLVESGGGV VQPGRSLRLSCA ASGFTFSSYDMS WVRQAPGKGLE WVAKVSSGGGS TYYLDTVQGRFT ISRDNSKNTLYL QMNSLRAEDTA VYYCARHLHGSF ASWGQGTTVTVS S	989	GFTF SSYD	990	VSSG GGST	991	ARHL HGSF AS	992
CD70	QAVVTQEPSL TVSPGGTVTL TCGLKSGSVT SDNFPTWYQQ TPGQAPRLLIY NTNTRHSGVP DRFSGSILGNK AALTITGAQA DDEAEYFCAL FISNPSVEFGG GTQLTVL	993	SGSV TSDN F	994	NTN	995	ALFI SNPS VEFG G	996	EVQLVESGGGLV QPGGSLRLSCAA SGFTFSVYYMN WVRQAPGKGLE WVSDINNEGGTT YYADSVKGRFTI SRDNSKNSLYLQ MNSLRAEDTAV YYCARDAGYSN HVPIFDSWGQGT LVTVSS	997	GFTF SVY Y	998	INNE GGTT	999	ARDA GYSN HVPI FDS	1000
CD73 (NT5E)	QSVLTQPPSAS GTPGQRVTISC SGSLSNIGRNP VNWYQQLPG TAPKLLIYLDN LRLSGVPDRFS GSKSGTSASL AISGLQSEDEA DYYCATWDD SHPGWTFGGG TKLTVL	1001	LSNI GRNP	1002	LDN	1003	ATW DDS HPG WT	1004	EVQLLESGGGLV QPGGSLRLSCAA SGFTFSSYAYSW VRQAPGKGLEW VSAISGSGGRTY YADSVKGRFTIS RDNSKNTLYLQ MNSLRAEDTAV YYCARLGYGRV DEWGRGTLVTVS S	1005	GFTF SSYA	1006	ISGS GGRT	1007	ARLG YGRV DE	1008
CD74	DIQLTQSPLSL PVTLGQPASIS CRSSQSLVHR NGNTYLHWF QQRPGQSPRL LIYTVSNRFSG VPDRFSGSGS GTDFTLKISRV EAEDVGVYFC SQSSHVPPTFG AGTRLEIK	1009	QSLV HRNG NTY	1010	TVS	1011	SQSS HVPP T	1012	QVQLQQSGSELK KPGASVKVSCKA SGYTFTNYGVN WIKQAPGQGLQ WMGWINPNTGE PTFDDDFKGRFA FSLDTSVSTAYL QISSLKADDTAV YFCSRSRGKNEA WFAYWGQGTLV TVSS	1013	GYTF TNY G	1014	INPN TGEP	1015	SRSR GKNE AWFA Y	1016

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
CEA	QTVLSQSPAIL SASPGEKVTM TCRASSSVTYI HWYQQKPGSS PKSWIYATSN LASGVPARFS GSGSGTSYSLT ISRVEAEDAAT YYCQHWSSKP PTFGGGTKLEI K	1017	SSVT Y	1018	ATS	1019	QHW SSKP PT	1020	EVKLVESGGGLV QPGGSLRLSCAT SGFTFTDYYMN WVRQPPGKALE WLGFIGNKANGY TTEYSASVKGRF TISRDKSQSILYL QMNTLRAEDSAT YYCTRDRGLRFY FDYWGQGTTLT VSS	1021	GFTF TDY Y	1022	IGNK ANGY TT	1023	TRDR GLRF YFDY	1024
CEA	DIQLTQSPSSL SASVGDRVTIT CKASQDVGTS VAWYQQKPG KAPKLLIYWT STRHTGVPSRF SGSGSGTDFTF TISSLQPE- DIAT YYCQQYSLYR SFGQGTKVEIK	1025	QDVG TS	1026	WTS	1027	QQY SLYR S	1028	EVQLVESGGGVV QPGRSLRLSCSAS GFDFTTYWMSW VRQAPGKGLEWI GEIHPDSSTINYA PSLKDRFTISRDN AKNTLFLQMDSL RPEDTGVYFCAS LYFGFPWFAYW GQGTPVTVSS	1029	GFDF TTY W	1030	IHPD SSTI	1031	ASLY FGFP WFAY	1032
Claudin-18.2	DIVMTQSPSSL TVTAGEKVTM SCKSSQSLLNS GNQKNYLTW YQQKPGQPPK LLIYWASTRES GVPDRFTGSG SGTDFTLTISS VQAEDLAVYY CQNDYSYPFT FGSGTKLEIK	1033	QSLL NSGN QKNY	1034	WAS	1035	QND YSYP FT	1036	QVQLQQPGAELV RPGASVKLSCKA SGYTFTSYWINW VKQRPGQGLEWI GNIYPSDSYTNY NQKFKDKATLTV DKSSSTAYMQLS SPTSEDSAVYYC TRSWRGNSFDY WGQGTTLTVSS	1037	GYTF TSY W	1038	IYPS DSYT	1039	TRSW RGNS FDY	1040
cMET	DIQMTQSPSSL SASVGDRVTIT CKSSQSLLYTS SQKNYLAWY QQKPGKAPKL LIYWASTRES GVPSRFSGSGS GTDFTLTISSL QPEDFATYYC QQYYAYPWTF GQGTKVEIK	1041	QSLL YTSS QKNY	1042	WAS	1043	QQY YAY PWT	1044	EVQLVESGGGLV QPGGSLRLSCAA SGYTFTSYWLH WVRQAPGKGLE WVGMIDPSNSDT RFNPNFKDRFTIS ADTSKNTAYLQ MNSLRAEDTAV YYCATYRSYVTP LDYWGQGTLVT VSS	1045	GYTF TSY W	1046	IDPS NSDT	1047	ATYR SYVT PLDY	1048

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
CRLR	QSVLTQPPSVS AAPGQKVTIS CSGSSSNIGNN YVSWYQQLPG TAPKLLIYDN NKRPSGIPDRF SGSKSGTSTTL GITGLQTGDE ADYYCGTWD SRLSAVVFGG GTKLTVL	1049	SSNI GNNY	1050	DNN	1051	GTW DSRL SAV V	1052	QVQLVESGGGV VQPGRSLRLSCA ASGFTFSSFGMH WVRQAPGKGLE WVAVISFDGSIK YSVDSVKGRFTIS RDNSKNTLFLQM NSLRAEDTAVYY CARDRLNYYDSS GYYHYKYYGMA VWGQGTTVTVSS	1053	GFTF SSFG	1054	ISFD GSIK	1055	ARDR LNYY DSSG YYHY KYYG MAV	1056
Dabiga-tran	DVVMTQSPLS LPVTLGQPASI SCKSSQSLLYT DGKTYLYWFL QRPGQSPRRLI YLVSKLDSGV PDRFSGSGSGT DFTLKISRVEA EDVGVYYCLQ STHFPHTFGG GTKVEIK	1057	QSLL YTDG KTY	1058	LVS	1059	LQST HFPH T	1060	QVQLQESGPGLV KPSETLSLTCTVS GFSLTSYIVDWIR QPPGKGLEWIGV IWAGGSTGYNSA LRSRVSITKDTSK NQFSLKLSSVTA ADTAVYYCASA AYYSYYNYDGF AYWGQGTLVTV SS	1061	GFSL TSYI	1062	IWAG GST	1063	ASAA YYSY YNYD GFAY	1064
DLL3	EIVMTQSPATL SVSPGERATLS CKASQSVSND VVWYQQKPG QAPRLLIYYAS NRYTGIPARFS GSGSGTEFTLT ISSLQSEDFAV YYCQQDYTSP WTFGQGTKLE IK	1065	QSVS ND	1066	YAS	1067	QQD YTSP WT	1068	QVQLVQSGAEV KKPGASVKVSCK ASGYTFTNYGM NWVRQAPGQGL EWMGWINTYTG EPTYADDFKGRV TMTTDTSTSTAY MELRSLRSDDTA VYYCARIGDSSPS DYWGQGTLVTV SS	1069	GYTF TNY G	1070	INTY TGEP	1071	ARIG DSSP SDY	1072
DLL4	EIVLTQSPATL SLSPGERATLS CRASQSVSSY LAWYQQKPG QAPRLLIYDAS NRATGIPARFS GSGSGTDFTLT ISSLEPEDFAV YYCQHRSNWP PTFGGGTKVEI K	1073	QSVS SY	1074	DAS	1075	QHRS NWP PT	1076	QVQLVESGGGV VQPGRSLRLSCA ASGFTFSSYGMH WVRQAPGKGLE WVSFLWYDGTN KNYVESVKGRFT ISRDNSKNMLYL EMNSLRAEDTAV YYCARDHDFRSG YEGWFDPWGQG TLVTVSS	1077	GFTF SSYG	1078	LWYD GTNK	1079	ARDH DFRS GYEG WFDP	1080

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
DLL4	DIVMTQSPDSL AVSLGERATIS CRASESVDNY GISFMKWFQQ KPGQPPKLLIY AASNQGSGVP DRFSGSGSGT DFTLTISSLQA EDVAVYYCQ QSKEVPWTFG GGTKVEIK	1081	ESVD NYGI SF	1082	AAS	1083	QQS KEVP WT	1084	QVQLVQSGAEV KKPGASVKISCK ASGYSFTAYYIH WVKQAPGQGLE WIGYISSYNGAT NYNQKFKGRVTF TTDTSTSTAYME LRSLRSDDTAVY YCARDYDYDVG MDYWGQGTLVT VSS	1085	GYSF TAY Y	1086	ISSY NGAT	1087	ARDY DYDV GMDY	1088
DNA/histone (H1) complex	ENVLTQSPAI MSASPGEKVT MTCRASSSVS SSYLHWYQQK SGASPKLWIYS TSNLASGVPA RFSGSGSGTSY SLTISSVEAED AATYYCQQYS GYPLTFGGGT KLEIK	1089	SSVS SSY	1090	STS	1091	QQY SGYP LT	1092	QVQLKESGPGLV APSQSLSITCTVS GFSLTDYGVRWI RQPPGKGLEWLG VIWGGGSTYYNS ALKSRLSISKDNS KSQVFLKMNSLQ TDDTAMYYCAK EKRRGYYYAMD YWGQGTSVTVSS	1093	GFSL TDY G	1094	IWGG GST	1095	AKEK RRGY YYAM DY	1096
EGFR	DILLTQSPVILS VSPGERVSFSC RASQSIGTNIH WYQQRTNGSP RLLIKYASE-SIS GIPSRFSGSGS GTDFTLSINSV ESEDIADYYC QQNNNWPTTF GAGTKLELK	1097	QSIG TN	1098	YAS	1099	QQN NNW PTT	1100	QVQLKQSGPGLV QPSQSLSITCTVS GFSLTNYGVHW VRQSPGKGLEWL GVIWSGGNTDYN TPFTSRLSINKDN SKSQVFFKMNSL QSNDTAIYYCAR ALTYYDYEFAY WGQGTLVTVSA	1101	GFSL TNY G	1102	IWSG GNT	1103	ARAL TYYD YEFA Y	1104
EGFR	DIQMTQSPSSL SASVGDRVTIT CQASQDISNY LNWYQQKPG KAPKLLIYDAS NLETGVPSRFS GSGSGTDFTFT ISSLQPEDIAT YFCQHFDHLP LAFGGGTKVE IK	1105	QDIS NY	1106	DAS	1107	QHF DHLP LA	1108	QVQLQESGPGLV KPSETLSLTCTVS GGSVSSGDYYW TWIRQSPGKGLE WIGHIYYSGNTN YNPSLKSRLTISI DTSKTQFSLKLSS VTAADTAIYYCV RDRVTGAFDIWG QGTMVTVSS	1109	GGS VSSG DYY	1110	IYYS GNT	1111	VRDR VTGA FDI	1112

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
EGFR	EIVMTQSPATL SLSPGERATLS CRASQSVSSY LAWYQQKPG QAPRLLIYDAS NRATGIPARFS GSGSGTDFTLT ISSLEPEDFAV YYCHQYGSTP LTFGGGTKAEI KR	1113	QSVS SY	1114	DAS	1115	HQY GSTP LT	1116	QVQLQESGPGLV KPSQTLSLTCTVS GGSISSGDYYWS WIRQPPGKGLEW IGYIYYSGSTDYN PSLKSRVTMSVD TSKNQFSLKVNS VTAADTAVYYC ARVSIFGVGTFD YWGQGTLVTVSS	1117	GGSI SSGD YY	1118	IYYS GST	1119	ARVS IFGV GTFD Y	1120
EGFR	DIQMTQSPSSL SASVGDRVTIT CRSSQNIVHSN GNTYLDWYQ QTPGKAPKLLI YKVSNRFSGV PSRFSGSGSGT DFTFTISSLQPE DIATYYCFQY SHVPWTFGQG TKLQIT	1121	QNIV HSNG NTY	1122	KVS	1123	FQYS HVP WT	1124	QVQLQQSGAEV KKPGSSVKVSCK ASGYTFTNYYIY WVRQAPGQGLE WIGGINPTSGGSN FNEKFKTRVTITV DESTNTAYMELS SLRSEDTAFYFC ARQGLWFDSDG RGFDFWGQGSTV TVSS	1125	GYTF TNY Y	1126	INPT SGGS	1127	ARQG LWFD SDGR GFDF W	1128
EGFR	IQLTQSPSSLS ASVGDRVTIT CRASQDISSAL VWYQQKPGK APKLLIYDASS LESGVPSARFS GSESGTDFTLT ISSLQPEDFAT YYCQQFNSYP LTFGGGTKVEI K	1129	QDIS SA	1130	DAS	1131	QQF NSYP LT	1132	QVQLVESGGGV VQPGRSLRLSCA ASGFTFSTYGMH WVRQAPGKGLE WVAVIWDDGSY KYYGDSVKGRFT ISRDNSKNTLYL QMNSLRAEDTA VYYCARDGITMV RGVMKDYFDYW GQGTLVTVSS	1133	GFTF STYG	1134	IWDD GSYK	1135	ARDG ITMV RGVM KDYF DY	1136
EGFR	DIQMTQSPSSL SASVGDRVTIT CRASQDINNY LAWYQHKPG KGPKLLIHYTS TLHPGIPSRFS GSGSGRDYSF SISSLEPE- DIAT YYCLQYDNLL YTFGQGTKLEI K	1137	QDIN NY	1138	YTS	1139	LQY DNLL YT	1140	QVQLVQSGAEV AKPGASVKLSCK ASGYTFTSYWM QWVKQRPGQGL ECIGTIYPGDGDT TYTQKFQGKATL TADKSSSTAYMQ LSSLRSEDSAVY YCARYDAPGYA MDYWGQGTLVT VSS	1141	GYTF TSY W	1142	IYPG DGDT	1143	ARYD APGY AMDY	1144

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
EGFR	DIQMTQSPSSL SASVGDRVTIT CSASSSVIYM YWYQQKPGK APKLLIYDTSN LASGVPSRFSG SGSGTDYTFTI SSLQPEDIATY YCQQWSSHIF TFGQGTKVEI K	1145	SSVT Y	1146	DTS	1147	QQW SSHI FT	1148	QVQLVQSGAEV KKPGASVKVSCK ASGYTFTSHWM HWVRQAPGQGL EWIGEFNPSNGR TNYNEKFKSKAT MTVDTSTNTAY MELSSLRSEDTA VYYCASRDYDY DGRYFDYWGQG TLVTVSS	1149	GYTF TSH W	1150	FNPS NGRT	1151	ASRD YDYD GRYF DY	1152
EGFR	DIQMTQSPSSL SASVGDRVTIT CRASQGINNY LNWYQQKPG KAPKRLIYNT NNLQTGVPSR FSGSGSGTEFT LTISSLQPEDF ATYYCLQHNS FPTFGQGTKLE IK	1153	QGIN NY	1154	NTN	1155	LQH NSFP T	1156	QVQLVQSGAEV KKPGSSVKVSCK ASGFTFTDYKIH WVRQAPGQGLE WMGYFNPNSGY STYAQKFQGRVT ITADKSTSTAYM ELSSLRSEDTAV YYCARLSPGGYY VMDAWGQGTTV TVSS	1157	GFTF TDY K	1158	FNPN SGYS	1159	ARLS PGGY YVMD AW	1160
EGFR HER3	DIQMTQSPSSL SASVGDRVTIT CRASQNIATD VAWYQQKPG KAPKLLIYSAS FLYSGVPSRFS GSGSGTDFTLT ISSLQPEDFAT YYCQQSEPEP YTFGQGTKVE IK	1161	QNIA TD	1162	SAS	1163	QQSE PEPY T	1164	EVQLVESGGGLV QPGGSLRLSCAA SGFTLSGDWIHW VRQAPGKGLEW VGEISAAGGYTD YADSVKGRFTIS ADTSKNTAYLQ MNSLRAEDTAV YYCARESRVSFE AAMDYWGQGTL VTVSS	1165	GFTL SGD W	1166	ISAA GGYT	1167	ARES RVSF EAAM DY	1168
EGFRvIII	DILMTQSPSSM SVSLGDTVSIT CHSSQDINSNI GWLQQRPGKS FKGLIYHGTN LDDEVPSRFSG SGSGADYSLTI SSLESEDFADY YCVQYAQFP WTFGGGTKLE IKA	1169	QDIN SN	1170	HGT	1171	VQY AQFP WT	1172	DVQLQESGPSLV KPSQSLSLTCTVT GYSITSDFAWNW IRQFPGNKLEWM GYISYSGNTRYN PSLKSRISITRDTS KNQFFLQLNSVTI EDTATYYCVTAG RGFPYWGQGTL VTVSS	1173	GYSI TSDF A	1174	ISYS GNT	1175	VTAG RGFP Y	1176

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
EGFRvIII	DIQMTQSPSS MSVSVGDRVT ITCHSSQDINS NIGWLQQKPG KSFKGLIYHGT NLDDGVPSRF SGSGSGTDYT LTISSLQPEDF ATYYCVQYA QFPWTFGGGT KLEIK	1177	QDIN SN	1178	HGT	1179	VQY AQFP WT	1180	QVQLQESGPGLV KPSQTLSLTCTVS GYSISSDFAWNW IRQPPGKGLEWM GYISYSGNTRYQ PSLKSRITISRDTS KNQFFLKLNSVT AADTATYYCVT AGRGFPYWGQG TLVTVSS	1181	GYSI SSDF A	1182	ISYS GNT	1183	VTAG RGFP Y	1184
EpCAM	ELVMTQSPSSL TVTAGEKVTM SCKSSQSLLNS GNQKNYLTW YQQKPGQPPK LLIYWASTRES GVPDRFTGSG SGTDFTLTISS VQAEDLAVYY CQNDYSYPLT FGAGTKLEIK	1185	QSLL NSGN QKNY	1186	WAS	1187	QND YSYP LT	1188	EVQLLEQSGAEL VRPGTSVKISCK ASGYAFTNYWL GWVKQRPGHGL EWIGDIHFPGSGN IHYNEKFKGKAT LTADKSSSTAYM QLSSLTFEDSAV YFCARLRNWDEP MDYWGQGTTVT VSS	1189	ASG YAFT N	1190	GDIH FPGS G	1191	FCAR LRNW DEPM DY	1192
EpCAM	ELQMTQSPSSL SASVGDRVTIT CRTSQSISSYL NWYQQKPGQ PPKLLIYWAST RESGVPDRFS GSGSGTDFTLT ISSLQPEDSAT YYCQQSYDIP YTFGQGTKLEI K	1193	QSIS SY	1194	WAS	1195	QQS YDIP YT	1196	EVQLLESGGGVV QPGRSLRLSCAA SGFTFSSYGMHW VRQAPGKGLEW VAVISYDGSNKY YADSVKGRFTIS RDNSKNTLYLQ MNSLRAEDTAV YYCAKDMGWGS GWRPYYYYGMD VWGQGTTVTVSS	1197	GFTF SSYG	1198	ISYD GSNK	1199	AKDM GWGS GWRP YYYY GMDV	1200
EpCAM	DIVLTQSPFSN PVTLGTSASIS CRSTKSLLHSN GITYLYWYLQ KPGQSPQLLIY QMSNLASGVP DRFSSSGSGTD FTLRISRVEAE DVGVYYCAQ NLEIPRTFGGG TKLEIK	1201	KSLL HSNG ITY	1202	QMS	1203	AQN LEIP RT	1204	QVKLQQSGPELK KPGETVKISCKAS GYTFTNYGMNW VKQAPGKGLKW MGWINTYTGEST YADDFKGRFAFS LETSASAAYLQIN NLKNEDTATYFC ARFAIKGDYWG QGTTVTVSS	1205	GYTF TNY G	1206	INTY TGES	1207	ARFA IKGD Y	1208

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
EpCAM	NIVMTQSPKS MSMSVGERVT LTCKASENVV TYVSWYQQKP EQSPKLLIYGA SNRYTGVPDR FTGSGSATDFT LTISSVQAEDL ADYHCGQGYS YPYTFGGGTK LEIK	1209	ENVV TY	1210	GAS	1211	GQG YSYP YT	1212	QVQLQQSGAELV RPGTSVKVSCKA SGYAFTNYLIEW VKQRPGQGLEWI GVINPGSGGTNY NEKFKGKATLTA DKSSSTAYMQLS SLTSDDSAVYFC ARDGPWFAYWG QGTLVTVSA	1213	GYA FTNY L	1214	INPG SGGT	1215	ARDG PWFA Y	1216
EpCAM	EIVMTQSPATL SVSPGERATLS CRASQSVSSN LAWYQQKPG QAPRLITYGAS TTASGIPARFS ASGSGTDFTLT ISSLQSEDFAV YYCQQYNNW PPAYTFGQGT KLEIK	1217	QSVS SN	1218	GAS	1219	QQY NNW PPAY T	1220	QVQLVQSGAEV KKPGSSVKVSCIC ASGGTFSSYAIS WVRQAPGQGLE WMGGIIPIFGTAN YAQKFQGRVTIT ADESTSTAYMEL SSLRSEDTAVYY CARGLLWNYWG QGTLVTVSS	1221	SGGT FSSY	1222	GIIP IFGT	1223	CARG LLWN Y	1224
EphA3	DIQMTQSPSFL SASVGDRVTIT CRASQGIISYL AWYQQKPEK APKRLIYAASS LQSGVPSRFSG SGSGTEFTLTI SSLQPEDFATY YCGQYANYPY TFGQGTKLEIK	1225	QGII SY	1226	AAS	1227	GQY ANY PYT	1228	QVQLVQSGAEV KKPGASVKVSCK ASGYTFTGYWM NWVRQAPGQGL EWMGDIYPGSGN TNYDEKFQGRVT MTRDTSISTAYM ELSRLRSDDTAV YYCARGGYYED FDSWGQGTTVTV SS	1229	GYTF TGY W	1230	IYPG SGNT	1231	ARGG YYED FDS	1232
ERGT(GalNAc) Tn Antigen	DIQLTQTPLSL PVSLGDQASIS CRSSQSLVHS NGNTYLHWY LQKPGQSPKL LIYKVSNRFSG VPDRFSGSGS GTDFTLKISSV EAEDLGVYFC SQSTHVPTFG GGTKLEIK	1233	QSLV HSNG NTY	1234	KVS	1235	SQST HVPT	1236	QVQLQQSGGGL VQPGGSMKIFCA ASGFTFSDAWM DWVRQSPEKGLE WVAEIRNKANN HETYYAESVKGR FTITRDDSKSRMS LQMNSLRAEDTG IYYCSGGKVRNA YWGQGTTVTVSS	1237	GFTF SDA W	1238	IRNK ANNH ET	1239	SGGK VRNA Y	1240

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
FLT1	EIVLTQSPGTL SLSPGERATLS CRASQSVSSSY LAWYQQKPG QAPRLLIYGAS SRATGIPDRFS GSGSGTDFTLT ISRLEPEDFAV YYCQQYGSSP LTFGGGTKVEI K	1241	QSVS SSY	1242	GAS	1243	QQY GSSP LT	1244	QAQVVESGGGV VQSGRSLRLSCA ASGFAFSSYGMH WVRQAPGKGLE WVAVIWYDGSN KYYADSVRGRFT ISRDNSENTLYLQ MNSLRAEDTAV YYCARDHYGSG VHHYFYYGLDV WGQGTTVTVSS	1245	GFAF SSYG	1246	IWYD GSNK	1247	ARDH YGSG VHHY FYYG LDV	1248
FOLR1	DIQLTQSPSSL SASVGDRVTIT CSVSSSISSNN LHWYQQKPG KAPKPWIYGT SNLASGVPSRF SGSGSGTDYT FTISSLQPE- DIA TYYCQQWSSY PYMYTFGQGT KVEIK	1249	SSIS SNN	1250	GTS	1251	QQW SSYP YMY T	1252	EVQLVESGGGVV QPGRSLRLSCAS GFTFSGYGLSWV RQAPGKGLEWV AMISSGGSYTYY ADSVKGRFAISR DNAKNTLFLQM DSLRPEDTGVYF CARHGDDPAWF AYWGQGTPVTV SS	1253	GFTF SGY G	1254	ISSG GSYT	1255	ARHG DDPA WFAY W	1256
FOLR1	DIVLTQSPLSL AVSLGQPAIIS CKASQSVSFA GTSLMHWYH QKPGQQPRLLI YRASNLEAGV PDRFSGSGSKT DFTLTISPVEA EDAATYYCQQ SREYPYTFGG GTKLEIK	1257	QSVS FAGT SL	1258	RAS	1259	QQSR EYPY T	1260	QVQLVQSGAEV VKPGASVKISCK ASGYTFTGYFMN WVKQSPGQSLE WIGRIHPYDGDT FYNQKFQGKATL TVDKSSNTAHME LLSLTSEDFAVY YCTRYDGSRAM DYWGQGTTVTV SS	1261	GYTF TGYF	1262	IHPY DGDT	1263	TRYD GSRA MDY	1264
frizzled family receptor (FZD)	DIELTQPPSVS VAPGQTARISC SGDNIGSFYV HWYQQKPGQ APVLVIYDKS NRPSGIPERFS GSNSGNTATL TISGTQAEDEA DYYCQSYANT LSLVFGGGTK LTVLG	1265	NIGS FY	1266	DKS	1267	QSY ANTL SLV	1268	EVQLVESGGGLV QPGGSLRLSCAA SGFTFSHYTLSW VRQAPGKGLEW VSVISGDGSYTY YADSVKGRFTISS DNSKNTLYLQM NSLRAEDTAVYY CARNFIKYVFAN WGQGTLVTVSS	1269	GFTF SHYT	1270	ISGD GSYT	1271	ARNF IKYV FAN	1272

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
Lewis Y	DVLMTQIPVS LPVSLGDQASI SCRSSQIIVHN NGNTYLEWYL QKPGQSPQLLI YKVSNRFSGV PDRFSGSGSGT DFTLKISRVEA EDLGVYYCFQ GSHVPFTFGSG TKLEIK	1273	QIIV HNNG NTY	1274	KVS	1275	FQGS HVPF T	1276	EVNLVESGGGLV QPGGSLKVSCVT SGFTFSDYYMY WVRQTPEKRLE WVAYISQGGDIT DYPDTVKGRFTIS RDNAKNSLYLQ MSRLKSEDTAM YYCARGLDDGA WFAYWGQGTLV TVSV	1277	GFTF SDY Y	1278	ISQG GDIT	1279	ARGL DDGA WFAY	1280
Lewis Y	DIQMTQSPSSL SASVGDRVTIT CRSSQRIVHSN GNTYLEWYQ QTPGKAPKLLI YKVSNRFSGV PSRFSGSGSGT DFTFTISSLQPE DIATYYCFQG SHVPFTFGQG TKLQIT	1281	QRIV HSNG NTY	1282	KVS	1283	FQGS HVPF T	1284	EVQLVESGGGVV QPGRSLRLSCSTS GFTFSDYYMYW VRQAPGKGLEW VAYMSNVGAITD YPDTVKGRFTISR DNSKNTLFLQMD SLRPEDTGVYFC ARGTRDGSWFA YWGQGTPVTVSS	1285	GFTF SDY Y	1286	MSNV GAIT	1287	ARGT RDGS WFAY	1288
Lewis X	DIVMTQAAFS NPVTLGTSASI SCRSSKSLLYS NGITYLYWYL QKPGQSPQLLI YQMSNLASGV PDRFSSSGSGT DFTLRISRVEA EDVGVYYCA QNLEVPWTFG GGTKLEIK	1289	KSLL YSNG ITY	1290	QMS	1291	AQN LEVP WT	1292	EVKLLESGGGLV QPGGSQKLSCAA SGFDFSGYWMS WVRQAPGKGLE WIGEINPDSSTIN YTPSLKDKFIISR DNAKNTLYLQM SKVRSEDTALYY CARETGTRFDYW GQGTTLTVSS	1293	SGFD FSGY	1294	EINP DSST	1295	CARE TGTR FDY	1296
GCGR	DIQMTQSPSSL SASVGDRVTIT CRASQGIRND LGWYQQKPG KAPKRLIYAA SSLQSGVPSRF SGSGSGTEFIL TVSSLQPEDFA TYYCLQYNSN PFTFGPGTKV DIK	1297	QGIR ND	1298	AAS	1299	LQY NSNP FT	1300	EVQLVESGGGLV QPGGSLRLSCAA SGFTFSNYLMNW VRQAPGKGLEW LANIQEDGIEKY YVDSVKGRFTIS RDNAKNSLYLQ MNSLRAEDTAV YYCAREPSHYDI LTGYDYYYGMD VWGQGTTVTVSS	1301	GFTF SNYL	1302	IQED GIEK	1303	AREP SHYD ILTG YDYY YGMD V	1304

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
GD2	EIVMTQSPATL SVSPGERATLS CRSSQSLVHR NGNTYLHWY LQKPGQSPKL LIHKVSNRFSG VPDRFSGSGS GTDFTLKISRV EAEDLGVYFC SQSTHVPPLTF GAGTKLELK	1305	QSLV HRNG NTY	1306	KVS	1307	SQST HVPP LT	1308	EVQLLQSGPELE KPGASVMISCKA SGSSFTGYNMN WVRQNIGKSLE WIGAIDPYYGGT SYNQKFKGRATL TVDKSSSTAYMH LKSLTSEDSAVY YCVSGMEYWGQ GTSVTVSS	1309	GSSF TGY N	1310	IDPY YGGT	1311	VSGM EY	1312
GD2	SIVMTQTPKFL LVSAGDRVTIT CKASQSVSND VTWYQQKAG QSPKLLIYSAS NRYSGVPDRF TGSGYGTAFT FTISTVQAEDL AVYFCQQDYS SFGGGTKLEIK	1313	QSVS ND	1314	SAS	1315	QQD YSS	1316	QVQLKESGPGLV APSQSLSITCTVS GFSVTNYGVHW VRQPPGKGLEWL GVIWAGGITNYN SAFMSRLSISKDN SKSQVFLKMNSL QIDDTAMYYCAS RGGHYGYALDY WGQGTSVTVSS	1317	GFSV TNY G	1318	IWAG GIT	1319	ASRG GHYG YALD Y	1320
GD2	EIVMTQTPATL SVSAGERVTIT CKASQSVSND VTWYQQKPG QAPRLLIYSAS NRYSGVPARF SGSGYGTEFTF TISSVQSEDFA VYFCQQDYSS FGQGTKLEIK	1321	QSVS ND	1322	SAS	1323	QQD YSS	1324	QVQLVESGPGVV QPGRSLRISCAVS GFSVTNYGVHW VRQPPGKGLEWL GVIWAGGITNYN SAFMSRLTISKDN SKNTVYLQMNSL RAEDTAMYYCA SRGGHYGYALD YWGQGTLVTVSS	1325	GFSV TNY G	1326	IWAG GIT	1327	ASRG GHYG YALD Y	1328
GD2 o-acetyl	DVVMTQTPLS LPVSLGDQASI SCRSSQSLLKN NGNTFLHWYL QKSGQSPKLLI YKVSNRLSGV PDRFSGSGSGT YFTLKISRVEA EDLGVYFCSQ STHIPYTFGGG TKLELK	1329	QSLL KNNG NTF	1330	KVS	1331	SQST HIPY T	1332	EVKLVESGGGLV LPGDSLRLSCATS KFTFTDYYMTW VRQPPRKALEQL GFIRNRANGYTT EYNPSVKGRFTIS RDNSQSILYLQM NTLRTEDSATYY CARVSNWAFDY WGQGTTLTVSS	1333	KFTF TDY Y	1334	IRNR ANGY TT	1335	ARVS NWAF DY	1336

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
GD3	DIQMTQITSL SVSLGDRVIIS CRASQDIGNFL NWYQQKPDG SLKLLIYYTSR LQSGVPSRFSG WGSGTDYSLT ISNLEEEDI- ATF FCQQGKTLPY TFGGGTKLEIK	1337	GFTF SNFG	1338	ISSG GSSI	1339	TRG GTGT RSLY YFD Y	1340	DVQLVESGGGLV QPGGSRKLSCAA SGFTFSNFGMHW VRQAPEKGLEW VAYISSGGSSINY ADTVKGRFTISR DNPKNTLFLQMT SLRSEDTAIYYCT RGGTGTRSLYYF DYWGQGATLIVS S	1341	QDIG NF	1342	YTS	1343	QQGK TLP	1344
GD3	DIQMTQTASS LPASLGDRVTI SCSASQDISNY LNWYQQKPD GTVKLLIFYSS NLHSGVPSRFS GGGSGTDYSL TISNLEPE- DIAT YFCHQYSKLP WTFGGGTKLE IK	1345	QDIS NY	1346	YSS	1347	HQY SKLP WT	1348	EVTLVESGGDFV KPGGSLKVSCAA SGFAFSHYAMSW VRQTPAKRLEW VAYISSGGSGTY YSDSVKGRFTISR DNAKNTLYLQM RSLRSEDSAMYF CTRVKLGTYYFD SWGQGTTLTVSS	1349	GFAF SHY A	1350	ISSG GSGT	1351	TRVK LGTY YFDS	1352
GM1	DIQMTQSPSSL SASVGDRVTIT CRASQGISSW LAWYQQKPE KAPKSLIYAAS SLQSGVPSRFS GSGSGTDFTLT ISSLQPEDFAT YYCQQYNSYP PTFGGGTKVEI K	1353	QGIS SW	1354	AAS	1355	QQY NSYP PT	1356	EVQLVESGGGLV QPGESLRLSCVA SGFTFSRYKMNW VRQAPGKGLEW VSYISRSGRDIYY ADSVKGRFTISR DNAKNSLYLQM NSLRDEDTAVYY CAGTVTTYYYYF GMDVWGHGTTV TVSS	1357	GFTF SRY K	1358	ISRS GRDI	1359	AGTV TTYY YYFG MDV	1360
GM1 fucosyl	DIQMTQSPSSL SASVGDRVTIT CRASQGISWL AWYQQKPEK APKSLIYAASS LQSGVPSRFSG SGSGTDFTLTI SSLQPEDFATY YCQQYNSYPP TFGGGTKVEI K	1361	QGIS W	1362	AAS	1363	QQY NSYP PT	1364	EVQLVESGGGLY QPGESLRLSCVA SGFTFSRYKMNW VRQAPGKGLLE WVSYISRSGRDIY YADSVKGRFTIS RDNAKNSLYLQ MNSLRDEDTAV YYCAGTVTTYY YYFGMDVWGHG TTVTVSS	1365	GFTF SRYK	1366	YISR SGRD	1367	CAGT VTTY YYYF GMDV	1368

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
GM1 fucosyl	DIQMTQSPSSL ASVGDRVTIT CRASQGISSW LAWYQQKPE KAPKSLIYAAS SLQSGVPSRFS GSGSGTDFTLT ISCLQPEDFAT YYCQQYNSYP PTFGGGTKVEI K	1369	QGIS SW	1370	AAS	1371	QQY NSYP PT	1372	EVQLVESGGGLV QPGESLRLSCVV SGFTFSRYKMNW VRQAPGKGLEWI SYISRSGRDIYYA DSVKGRFTISRD NAKNSLYLQMSS LRDEDTAVYYCA GTVTTYYYYFG MDVWGLGITVT VSS	1373	GFTF SRY K	1374	ISRS GRDI	1375	AGTV TTYY YYFG MDVW G	1376
GM1 fucosyl	DIQMTQSPSSL SASVGDRVTIT CRASQGISSW LAWYQQKPE KAPKSLIYAAS LQSGVPSRFSG SGSGTDFTLTI SSLQPEDFATY YCQQYNSYPP TFGGGTKVEI K	1377	QGIS SW	1378	AA	1379	QQY NSYP PT	1380	EVQLVESGGGSV QPGESLRLSCVA SGFTFSRYKMNW VRQAPGKGLEW VSYISRSGRDIYY ADSVKGRFTISR DNAKNSLYLQM NSLRDEDTAVYY CAGTVTTYYYDF GMDVWGQGTTV TVSS	1381	GFTF SRY K	1382	ISRS GRDI	1383	AGTV TTYY YDFG MDV	1384
GM2	QIVLTQSPAIM SASPGEKVTIT CSASSSVSYM HWFQQKPGTS PKLWIYSTSNL ASGVPARFSG SGSGTSYSLTI SRMEAEDAAT YYCQQRSSYP YTFGGGTKLEI K	1385	SSVS Y	1386	STS	1387	QQRS SYPY T	1388	EVQLQQSGPELV KPGASVKISCKA SGYTFTDYNMD WVKQSHGKSLE WIGYIYPNNGGT GYNQKFKSKATL TVDKSSSTAYME LHSLTSEDSAVY YCATYGHYYGY MFAYWGQGTLV TVSA	1389	GYTF TDY N	1390	IYPN NGGT	1391	ATYG HYYG YMFA Y	1392
GPA33	DIVMTQSQKF MSTSVGDRVS ITCKASQNVR TVVAWYQQK PGQSPKTLIYL ASNRHTGVPD RFTGSGSGTDF TLTISNVQSED LADYFCLQHW SYPLTFGSGTK LEVK	1393	QNVR TV	1394	LAS	1395	LQH WSY PLT	1396	EVKLVESGGGLV KPGGSLKLSCAA SGFAFSTYDMSW VRQTPEKRLEWV ATISSGGSYTYYL DSVKGRFTISRDS ARNTLYLQMSSL RSEDTALYYCAP TTVVPFAYWGQ GTLVTVSA	1397	GFAF STYD	1398	ISSG GSYT	1399	APTT VVPF AY	1400

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
GPNMB	EIVMTQSPATL SVSPGERATLS CRASQSVDNN LVWYQQKPG QAPRLLIYGAS TRATGIPARFS GSGSGTEFTLT ISSLQSEDFAV YYCQQYNNW PPWTFGQGTK VEIK	1401	QSVD NN	1402	GAS	1403	QQY NNW PPWT	1404	QVQLQESGPGLV KPSQTLSLTCTVS GGSISSFNYYWS WIRHHPGKGLE WIGYIYYSGSTYS NPSLKSRVTISVD TSKNQFSLTLSSV TAADTAVYYCA RGYNWNYFDYW GQGTLVTVSS	1405	GGSI SSFN YY	1406	IYYS GST	1407	ARGY NWNY FDY	1408
GUCY2C	EIVMTQSPATL SVSPGERATLS CRASQSVSRN LAWYQQKPG QAPRLLIYGAS TRATGIPARFS GSGSGTEFTLT IGSLQSEDFAV YYCQQYKTW PRTFGQGTNV EIK	1409	QSVS RN	1410	GAS	1411	QQY KTW PRT	1412	QVQLQQWGAGL LKPSETLSLTCAV FGGSFSGYYWS WIRQPPGKGLEW IGEINHRGNTND NPSLKSRVTISVD TSKNQFALKLSS VTAADTAVYYC ARERGYTYGNFD HWGQGTLVTVSS	1413	GGSF SGY Y	1414	INHR GNT	1415	ARER GYTY GNFD H	1416
HER2	DIQMTQSPSSL SASVGDRVTIT CRASQDVNTA VAWYQQKPG KAPKLLIYSAS FLYSGVPSRFS GSRSGTDFTLT ISSLQPEDFAT YYCQQAYTTP PTFGQGTKVEI K	1417	QDVN TA	1418	SAS	1419	QQA YTTP PT	1420	EVQLVESGGGLV QPGGSLRLSCAA SGFNIKDTYIHW VRQAPGKGLEW VARIYPTNGYTR YADSVKGRFTIS ADTSKNTAYLQ MNSLRAEDTAV YYCSRWGGDGF YAMDYWGQGTL VTVSS	1421	GFNI KDT Y	1422	IYPT NGYT	1423	SRWG GDGF YAMD Y	1424
HER2	DIQMTQSPSSL SASVGDRVTIT CRASQDVNTA VAWYQQKPG KAPKLLIYSAS FLYSGVPSRFS GSRSGTDFTLT ISSLQPEDFAT YYCQQHYTTP PTFGQGTKVEI K	1425	QDVN TA	1426	SAS	1427	QQH YTTP PT	1428	EVQLVESGGGLV QPGGSLRLSCAA SGFNIKDTYIHW VRQAPGKGLEW VARIYPTNGYTR YADSVKGRFTIS ADTSKNTAYLQ MNSLRAEDTAV YYCSRWGGDGF YAMDYWGQGTL VTVSS	1429 KDT	GFNI Y	1430	IYPT NGYT	1431 GDGF	SRWG YAMD Y	1432

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
HER2	DIQMTQSPSSL SASVGDRVTIT CKASQDVSIG VAWYQQKPG KAPKLLIYSAS YRYTGVPSRF SGSGSGTDFTL TISSLQPEDFA TYYCQQYYIY PYTFGQGTKV EIK	1433	QDVS IG	1434	SAS	1435	QQY YIYP YT	1436	EVQLVESGGGLV QPGGSLRLSCAA SGFTFTDYTMDW VRQAPGKGLEW VADVNPNSGGSI YNQRFKGRFTLS VDRSKNTLYLQ MNSLRAEDTAV YYCARNLGPSFY FDYWGQGTLVT VSS	1437	GFTF TDY T	1438	VNPN SGGS	1439	ARNL GPSF YFDY W	1440
HER2	QSVLTQPPSVS GAPGQRVTISC TGSSSNIGAGY GVHWYQQLP GTAPKLLIYG NTNRPSGVPD RFSGFKSGTSA SLAITGLQAED EADYYCQSYD SSLSGWVFGG GTKLTVL	1441	SSNI GAGY G	1442	GNT	1443	QSY DSSL SGW V	1444	QVQLVESGGGLV QPGGSLRLSCAA SGFTFRSYAMSW VRQAPGKGLEW VSAISGRGDNTY YADSVKGRFTIS RDNSKNTLYLQ MNSLRAEDTAV YYCAKMTSNAF AFDYWGQGTLV TVSS	1445	GFTF RSY A	1446	ISGR GDNT	1447	AKMT SNAF APDY	1448
HER3	QSALTQPASV SGSPGQSITISC TGTSSDVGSY NVVSWYQQH PGKAPKLIIYE VSQRPSGVSN RFSGSKSGNT ASLTISGLQTE DEADYYCCSY AGSSIFVIFGG GTKVTVL	1449	SSDV GSYN V	1450	EVS	1451	CSYA GSSI FVI	1452	EVQLLESGGGLV QPGGSLRLSCAA SGFTFSHYVMA WVRQAPGKGLE WVSSISSSGGWT LYADSVKGRFTIS RDNSKNTLYLQ MNSLRAEDTAV YYCTRGLKMATI FDYWGQGTLVT VSS	1453	GFTF SHY V	1454	ISSS GGWT	1455	TRGL KMAT IFDY	1456
HER3	DIQMTQSPSSL SASVGDRVTIT CRASQGISNW LAWYQQKPG KAPKLLIYGAS SLQSGVPSRFS GSGSGTDFTLT ISSLQPEDFAT YYCQQYSSFP TTFGQGTKVEI K	1457	QGIS NW	1458	GAS	1459	QQY SSFP TT	1460	EVQLLESGGGLV QPGGSLRLSCAA SGFTFSSYAMSW VRQAPGKGLEW VSAINSQGKSTY YADSVKGRFTIS RDNSKNTLYLQ MNSLRAEDTAV YYCARWGDEGF DIWGQGTLVTVS S	1461	GFTF SSYA	1462	INSQ GKST	1463	ARWG DEGF DI	1464

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
HER3	DIEMTQSPDSL AVSLGERATIN CRSSQSVLYSS SNRNYLAWY QQNPGQPPKL LIYWASTRES GVPDRFSGSG SGTDFTLTISS LQAEDVAVYY CQQYYSTPRT FGQGTKVEIK	1465	QSVL YSSS NRNY	1466	WAS	1467	QQY YSTP RT	1468	QVQLQQWGAGL LKPSETLSLTCAV YGGSFSGYYWS WIRQPPGKGLEW IGEINHSGSTNYN PSLKSRVTISVET SKNQFSLKLSSVT AADTAVYYCAR DKWTWYFDLWG RGTLVTVSS	1469	GGSF SGY Y	1470	INHS GST	1471	ARDK WTWY FDL	1472
HER3	DIVMTQSPDSL AVSLGERATIN CKSSQSVLNS GNQKNYLTW YQQKPGQPPK LLIYWASTRES GVPDRFSGSG SGTDFTLTISS LQAEDVAVYY CQSDYSYPYT FGQGTKLEIK	1473	QSVL NSGN QKNY	1474	WAS	1475	QSD YSYP YT	1476	QVQLVQSGAEV KKPGASVKVSCK ASGYTFRSSYISW VRQAPGQGLEW MGWIYAGTGSPS YNQKLQGRVTM TTDTSTSTAYME LRSLRSDDTAVY YCARHRDYYSNS LTYWGQGTLVT VSS	1477	GYTF RSSY	1478	IYAG TGSP	1479	ARHR DYYS NSLT Y	1480
HER3	YELTQDPAVS VALGQTVRIT CQGDSLRSYY ASWYQQKPG QAPVLVIYGK NNRPSGIPDRF SGSTSGNSASL TITGAQAEDE ADYYCNSRDS PGNQWVFGG GTKVTVL	1481	SLRS YY	1482	GKN	1483	NSRD SPGN QWV	1484	QVQLVQSGGGL VQPGGSLRLSCA ASGFTFDDYAMH WVRQAPGKGLE WVAGISWDSGST GYADSVKGRFTI SRDNAKNSLYLQ MNSLRAEDTALY YCARDLGAYQW VEGFDYWGQGT LVTVSS	1485	GFTF DDY A	1486	ISWD SGST	1487	ARDL GAYQ WVEG FDY	1488
HGFR (cMET)	DIVMTQSPDSL AVSLGERATIN CKSSESVDSY ANSFLHWYQQ KPGQPPKLLIY RASTRESGVP DRFSGSGSGT DFTLTISSLQA EDVAVYYCQ QSKEDPLTFG GGTKVEIK	1489	ESVD SYAN SF	1490	RAS	1491	QQS KEDP LT	1492	QVQLVQSGAEV KKPGASVKVSCK ASGYIFTAYTMH WVRQAPGQGLE WMGWIKPNNGL ANYAQKFQGRV TMTRDTSISTAY MELSRLRSDDTA VYYCARSEITTEF DYWGQGTLVTV SS	1493	GYIF TAY T	1494	IKPN NGLA	1495	ARSE ITTE FDY	1496

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
HGFR (cMET)	DIQMTQSPSSL SASVGDRVTIT CSVSSSVSSIY LHWYQQKPG KAPKLLIYSTS NLASGVPSRFS GSGSGTDFTLT ISSLQPEDFAT YYCQVYSGYP LTFGGGTKVEI K	1497	SSVS SIY	1498	STS	1499	QVY SGYP LT	1500	QVQLVQSGAEV KKPGASVKVSCK ASGYTFTDYYM HWVRQAPGQGL EWMGRVNPNRR GTTYNQKFEGRV TMTTDTSTSTAY MELRSLRSDDTA VYYCARANWLD YWGQGTTVTVSS	1501	GYTF TDY Y	1502	VNPN RRGT	1503	ARAN WLDY	1504
IgHe	DIQLTQSPSSL SASVGDRVTIT CRASQSVDYD GDSYMNWYQ QKPGKAPKLLI YAASYLESGV PSRFSGSGSGT DFTLTISSLQP EDFATYYCQQ SHEDPYTFGQ GTKVEIK	1505	QSVD YDGD SY	1506	AAS	1507	QQS HEDP YT	1508	EVQLVESGGGLV QPGGSLRLSCAV SGYSITSGYSWN WIRQAPGKGLE WVASITYDGSTN YNPSVKGRITISR DDSKNTFYLQM NSLRAEDTAVYY CARGSHYFGHW HFAVWGQGTLV TVSS	1509	GYSI TSGY S	1510	ITYD GST	1511	ARGS HYFG HWHF AV	1512
IgHe	EIVMTQSPATL SVSPGERATLS CRASQSIGTNI HWYQQKPGQ APRLLIYYASE SISGI-PARFSGS GSGTEFTLTIS SLQSEDFAVY YCQQSWSWPT TFGGGTKVEI K	1513	QSIG TN	1514	YAS	1515	QQS WSW PTT	1516	QVQLVQSGAEV MKPGSSVKVSCK ASGYTFSWYWL EWVRQAPGHGL EWMGEIDPGTFT TNYNEKFKARVT FTADTSTSTAYM ELSSLRSEDTAV YYCARFSHFSGS NYDYFDYWGQG TLVTVSS	1517	GYTF SWY W	1518	IDPG TFTT	1519	ARFS HFSG SNYD YFDY W	1520
IGLF2	QSVLTQPPSVS AAPGQKVTIS CSGSSSNIENN HVSWYQQLPG TAPKLLIYDN NKRPSGIPDRF SGSKSGTSATL GITGLQTGDE ADYYCETWD TSLSAGRVFG GGTKLTVL	1521	SSNI ENNH	1522	DNN	1523	ETW DTSL SAGR V	1524	QVQLVQSGAEV KKPGASVKVSCK ASGYTFTSYDIN WVRQATGQGLE WMGWMNPNSG NTGYAQKFQGR VTMTRNTSISTA YMELSSLRSEDT AVYYCARDPYY YYYGMDVWGQ GTTVTVSS	1525	GYTF TSYD	1526	MNPN SGNT	1527	ARDP YYYY YGMD V	1528

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
Kalli-kreins	DIQMTQSPSTL SASVGDRVTIT CRASQSISSWL AWYQQKPGK APKLLIYKAST LESGVPSRFSG SGSGTEFTLTI SSLQPDDFAT YYCQQYNTY WTFGQGTKVE IK	1529	QSIS SW	1530	KAS	1531	QQY NTY WT	1532	EVQLLESGGGLV QPGGSLRLSCAA SGFTFSHYIMMW VRQAPGKGLEW VSGIYSSGGITVY ADSVKGRFTISR DNSKNTLYLQM NSLRAEDTAVYY CAYRRIGVPRRD EFDIWGQGTMVT VSS	1533	GFTF SHYI	1534	IYSS GGIT	1535	AYRR IGVP RRDE FDI	1536
KIRDL1/2/3	EIVLTQSPVTL SLSPGERATLS CRASQSVSSY LAWYQQKPG QAPRLLIYDAS NRATGIPARFS GSGSGTDFTLT ISSLEPEDFAV YYCQQRSNW MYTFGQGTKL EIK	1537	QSVS SY	1538	DAS	1539	QQRS NWM YT	1540	QVQLVQSGAEV KKPGSSVKVSCK ASGGTFSFYAIS WVRQAPGQGLE WMGGFIPIFGAA NYAQKFQGRVTI TADESTSTAYME LSSLRSDDTAVY YCARIPSGSYYY DYDMDVWGQGT TVTVSS	1541	GGTF SFYA	1542	FIPI FGAA	1543	ARIP SGSY YYDY DMDV	1544
LINGO1	DIQMTQSPAT LSLSPGERATL SCRASQSVSSY LAWYQQKPG QAPRLLIYDAS NRATGIPARFS GSGSGTDFTLT ISSLEPEDFAV YYCQQRSNWP MYTFGQGTKL EIK	1545	QSVS SY	1546	DAS	1547	QQRS NWP MYT	1548	EVQLLESGGGLV QPGGSLRLSCAA SGFTFSAYEMKW VRQAPGKGLEW VSVIGPSGGFTFY ADSVKGRFTISR DNSKNTLYLQM NSLRAEDTAVYY CATEGDNDAFDI WGQGTTVTVSS	1549	GFTF SAYE	1550	IGPS GGFT	1551	ATEG DNDA FDI	1552
LOXL2	DIVMTQTPLSL SVTPGQPASIS CRSSKSLLHSN GNTYLYWFLQ KPGQSPQFLIY RMSNLASGVP DRFSGSGSGT DFTLKISRVEA EDVGVYYCM QHLEYPYTFG GGTKVEIK	1553	KSLL HSNG NTY	1554	RMS	1555	MQH LEYP YT	1556	QVQLVQSGAEV KKPGASVKVSCK ASGYAFTYYLIE WVRQAPGQGLE WIGVINPGSGGT NYNEKFKGRATI TADKSTSTAYME LSSLRSEDTAVYF CARNWMNFDY WGQGTTVTVSS	1557	GYA FTYY L	1558	INPG SGGT	1559	ARNW MNFD Y	1560

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
Ly6/PLAUR domain-containing protein 3	ESVLTQPPSVS GAPGQRVTISC TGSSSNIGAGY VVHWYQQLP GTAPKLLIYD NNKRPSGVPD RFSGSKSGTSA SLAISGLRSED EADYYCAAW DDRLNGPVFG GGTKLTVL	1561	SSNI GAGY V	1562	DNN	1563	AAW DDR LNGP V	1564	EVQLLESGGGLV QPGGSLRLSCAA SGFTFSNAWMS WVRQAPGKGLE WVSYISSSGSTIY YADSVKGRFTIS RDNSKNTLYLQ MNSLRAEDTAV YYCAREGLWAF DYWGQGTLVTV SS	1565	GFTF SNA W	1566	ISSS GSTI	1567	AREG LWAF DY	1568
MADCAM1	DIVMTQTPLSL SVTPGQPASIS CKSSQSLLHT DGTTYLYWYL QKPGQPPQLLI YEVSNRFSGV PDRFSGSGSGT DFTLKISRVEA EDVGIYYCMQ NIQLPWTFGQ GTKVEIK	1569	QSLL HTDG TTY	1570	EVS	1571	MQNI QLP WT	1572	QVQLVQSGAEV KKPGASVKVSCK ASGYTFTSYGIN WVRQAPGQGLE WMGWISVYSGN TNYAQKVQGRV TMTADTSTSTAY MDLRSLRSDDTA VYYCAREGSSSS GDYYYGMDVW GQGTTVTVSS	1573	GYTF TSYG	1574	ISVY SGNT	1575	AREG SSSS GDYY YGMD V	1576
MAG	DIVMTQSPDSL AVSLGERATIN CKSSHSVLYSS NQKNYLAWY QQKPGQPPKL LIYWASTRES GVPDRFSGSG SGTDFTLTISS LQAEDVAVYY CHQYLSSLTF GQGTKLEIK	1577	HSVL YSSN QKNY	1578	WAS	1579	HQY LSSL T	1580	QVQLVQSGSELK KPGASVKVSCKA SGYTFTNYGMN WVRQAPGQGLE WMGWINTYTGE PTYADDFTGRFV FSLDTSVSTAYL QISSLKAEDTAV YYCARNPINYYG INYEGYVMDYW GQGTLVTVSS	1581	GYTF TNY G	1582	INTY TGEP	1583	ARNP INYY GINY EGYV MDY	1584
Mesothelin	DIALTQPASVS GSPGQSITISCT GTSSDIGGYNS VSWYQQHPG KAPKLMIYGV NNRPSGVSNR FSGSKSGNTAS LTISGLQAEDE ADYYCSSYDI ESATPVFGGG TKLTVL	1585	SSDI GGYN S	1586	GVN	1587	SSYD IESA TPV	1588	QVELVQSGAEVK KPGESLKISCKGS GYSFTSYWIGWV RQAPGKGLEWM GIIDPGDSRTRYS PSFQGQVTISADK SISTAYLQWSSLK ASDTAMYYCAR GQLYGGTYMDG WGQGTLVTVSS	1589	GYSF TSY W	1590	IDPG DSRT	1591	ARGQ LYGG TYMD G	1592

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
Meso-thelin	DIELTQSPAIM SASPGEKVTM TCSASSSVSY MHWYQQKSG TSPKRWIYDTS KLASGVPGRF SGSGSGNSYSL TISSVEAEDDA TYYCQQWSK HPLTFGSGTK VEIK	1593	SSVS Y	1594	DTS	1595	QQW SKHP LT	1596	QVQLQQSGPELE KPGASVKISCKA SGYSFTGYTMN WVKQSHGKSLE WIGLITPYNGASS YNQKFRGKATLT VDKSSSTAYMDL LSLTSEDSAVYFC ARGGYDGRGFD YWGSGTPVTVSS	1597	GYSF TGY T	1598	ITPY NGAS	1599	ARGG YDGR GFDY	1600
MT1-MMP (MMP14)	DIQMTQSPSSL SASVGDRVTIT CKASQDVRNT VAWYQQKPG KAPKLLIYSSS YRNTGVPDRF SGSGSGTDFTL TISSLQAEDVA VYYCQQHYIT PYTFGGGTKV EIK	1601	QDVR NT	1602	SSS	1603	QQH YITP YT	1604	QVQLQESGPGLV KPSETLSLTCTVS GFSLLSYGVHWV RQPPGKGLEWLG VIWTGGTTNYNS ALMSRFTISKDDS KNTVYLKMNSL KTEDTAIYYCAR YYYGMDYWGQ GTLVTVSS	1605	GFSL LSYG	1606	IWTG GTT	1607	ARYY YGMD Y	1608
MUC1	DIQLTQSPSSL SASVGDRVTM TCSASSSVSSS YLYWYQQKP GKAPKLWIYS TSNLASGVPA RFSGSGSGTDF TLTISSLQPED SASYFCHQWN RYPYTFGGGT RLEIK	1609	SSVS SSY	1610	STS	1611	HQW NRYP YT	1612	QVQLQQSGAEV KKPGASVKVSCE ASGYTFPSYVLH WVKQAPGQGLE WIGYINPYNDGT QYNEKFKGKATL TRDTSINTAYME LSRLRSDDTAVY YCARGFGGSYGF AYWGQGTLVTV SS	1613	GYTF PSYV	1614	INPY NDGT	1615	ARGF GGSY GFAY	1616
Mucin 5AC	QVVLTQSPVI MSASPGEKVT MTCSASSSISY MYWYQQKPG TSPKRWIYDTS KLASGVPARF SGSGSGTSYSL TISNMEAGDA ATYYCHQRDS YPWTFGGGIN LEIK	1617	SSIS Y	1618	DTS	1619	HQR DSYP WT	1620	QVQLKESGPDLV APSQSLSITCTVS GFSLSKFGVNWV RQPPGKGLEWLG VIWGDGSTSYNS GLISRLSISKENS KSQVFLKLNSLQ ADDTATYYCVKP GGDYWGHGTSV TVSS	1621	GFSL SKFG	1622	IWGD GST	1623	VKPG GDY	1624

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
NaPi2b	DIQMTQSPSSL SASVGDRVTIT CRSSETLVHSS GNTYLEWYQ QKPGKAPKLLI YRVSNRFSGV PSRFSGSGSGT DFTLTISSLQP EDFATYYCFQ GSFNPLTFGQ GTKVEIK	1625	ETLV HSSG NTY	1626	RVS	1627	FQGS FNPL T	1628	EVQLVESGGGLV QPGGSLRLSCAA SGFSFSDFAMSW VRQAPGKGLEW VATIGRVAFHTY YPDSMKGRFTIS RDNSKNTLYLQ MNSLRAEDTAV YYCARHRGFDV GHFDFWGQGTL VTVSS	1629	GFSF SDFA	1630	IGRV AFHT	1631	ARHR GFDV GHFD F	1632
NeuGc-GM3	DIVMTQSHKF MSTSVGDRVS ITCKASQDVST AVAWYQQKP GQSPKLLIYSA SYRYTGVPDR FTGSGSGTDFT FTISSVQAEDL AVYYCQQHYS TPWTFGGGTK LELK	1633	QDVS TA	1634	SAS	1635	QQH YSTP WT	1636	EVQLKESGPGLV APSQSLSITCTVS GFSLSRYSVHWV RQPPGKGLEWLG MIWGGGSTDYNS ALKSRLSISKDNS KSQVFLKMNSLQ TDDTAMYYCAR SGVREGRAQAW FAYWGQGTLVT VSA	1637	GFSL SRYS	1638	IWGG GST	1639	ARSG VREG RAQA WFAY	1640
NKG2A	DIQMTQSPSSL SASVGDRVTIT CRASENIYSYL AWYQQKPGK APKLLIYNAK TLAEGVPSRFS GSGSGTDFTLT ISSLQPEDFAT YYCQHHYGTP RTFGGGTKVEI K	1641	ENIY SY	1642	NAK	1643	QHH YGTP RT	1644	QVQLVQSGAEV KKPGASVKVSCK ASGYTFTSYWM NWVRQAPGQGL EWMGRIDPYDSE THYAQKLQGRV TMTTDTSTSTAY MELRSLRSDDTA VYYCARGGYDF DVGTLYWFFDV WGQGTTVTVSS	1645	GYTF TSY W	1646	IDPY DSET	1647	ARGG YDFD VGTL YWFF DV	1648
notch	QAVVTQEPSL TVSPGGTVTL TCRSSTGAVT TSNYANWFQQ KPGQAPRTLIG GTNNRAPGVP ARFSGSLLGG KAALTLSGAQ PEDEAEYYCA LWYSNHWVF GGGTKLTV	1649	TGAV TTSN Y	1650	GTN	1651	ALW YSN HWV	1652	QVQLVQSGAEV KKPGASVKISCK VSGYTLRGYWIE WVRQAPGKGLE WIGQILPGTGRT NYNEKFKGRVT MTADTSTDTAY MELSSLRSEDTA VYYCARFDGNY GYYAMDYWGQ GTTVTVSS	1653	GAS VKIS CKV S	1654	ILPG TGRT	1655	ARFD GNYG YYAM DYW	1656

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
NOTCH2/ NOTCH3 recep- tors	DIVLTQSPATL SLSPGERATLS CRASQSVRSN YLAWYQQKP GQAPRLLIYG ASSRATGVPA RFSGSGSGTDF TLTISSLEPEDF AVYYCQQYSN FPITFGQGTKV EIK	1657	QSVR SNY	1658	GAS	1659	QQY SNFP IT	1660	EVQLVESGGGLV QPGGSLRLSCAA SGFTFSSSGMSW VRQAPGKGLEW VSVIASSGSNTYY ADSVKGRFTISR DNSKNTLYLQM NSLRAEDTAVYY CARSIFYTTWGQ GTLVTVSS	1661	GFTF SSSG	1662	IASS GSNT	1663	ARSI FYTT	1664
NRP1	DIQMTQSPSSL SASVGDRVTIT CRASQYFSSY LAWYQQKPG KAPKLLIYGAS SRASGVPSRFS GSGSGTDFTLT ISSLQPEDFAT YYCQQYLGSP PTFGQGTKVEI K	1665	QYFS SY	1666	GAS	1667	QQY LGSP PT	1668	EVQLVESGGGLV QPGGSLRLSCAA SGFTFSSYAMSW VRQAPGKGLEW VSQISPAGGYTN YADSVKGRFTIS ADTSKNTAYLQ MNSLRAEDTAV YYCARGELPYYR MSKVMDVWGQ GTLVTVSS	1669	GFTF SSYA	1670	ISPA GGYT	1671	ARGE LPYY RMSK VMDV	1672
oxLDL	QSVLTQPPSAS GTPGQRVTISC SGSNTNIGKN YVSWYQQLPG TAPKLLIYANS NRPSGVPDRFS GSKSGTSASL AISGLRSEDEA DYYCASWDA SLNGWVFGGG TKLTVL	1673	NTNI GKNY	1674	ANS	1675	ASW DASL NGW V	1676	EVQLLESGGGLV QPGGSLRLSCAA SGFTFSNAWMS WVRQAPGKGLE WVSSISVGGHRT YYADSVKGRSTI SRDNSKNTLYLQ MNSLRAEDTAV YYCARIRVGPSG GAFDYWGQGTL VTVSS	1677	GFTF SNA W	1678	ISVG GHRT	1679	ARIR VGPS GGAF DY	1680
P-selectin	EIVLTQSPATL SLSPGERATLS CRASQSVSSY LAWYQQKPG QAPRLLIYDAS NRATGIPARFS GSGSGTDFTLT ISSLEPEDFAV YYCQQRSNWP LTFGGGTKVEI K	1681	QSVS SY	1682	DAS	1683	QQRS NWP LT	1684	EVQLVESGGGLV RPGGSLRLSCAA SGFTFSNYDMH WVRQATGKGLE WVSAITAAGDIY YPGSVKGRFTISR ENAKNSLYLQM NSLRAGDTAVYY CARGRYSGSGSY YNDWFDPWGQG TLVTVSS	1685	GFTF SNY D	1686	ITAA GDI	1687	ARGR YSGS GSYY NDWF DP	1688

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
PCSK9	DIVMTQSPDSL AVSLGERATIN CKSSQSVLYR SNNRNFLGWY QQKPGQPPNL LIYWASTRES GVPDRFSGSG SGTDFTLTISS LQAEDVAVYY CQQYYTTPYT FGQGTKLEIK	1689	QSVL YRSN NRNF	1690	WAS	1691	QQY YTTP YT	1692	EVQLVESGGGLV QPGGSLRLSCAA SGFTFNNYAMN WVRQAPGKGLD WVSTISGSGGTT NYADSVKGRFIIS RDSSKHTLYLQM NSLRAEDTAVYY CAKDSNWGNFD LWGRGTLVTVSS	1693	GFTF NNY A	1694	ISGS GGTT	1695	AKDS NWGN FDL	1696
PCSK9	ESALTQPASVS GSPGQSITISCT GTSSDVGGYN SVSWYQQHPG KAPKLMIYEV SNRPSGVSNRF SGSKSGNTAS LTISGLQAEDE ADYYCNSYTS TSMVFGGGTK LTVL	1697	SSDV GGYN S	1698	EVS	1699	NSYT STSM V	1700	EVQLVQSGAEVK KPGASVKVSCKA SGYTLTSYGISW VRQAPGQGLEW MGWVSFYNGNT NYAQKLQGRGT MTTDPSTSTAYM ELRSLRSDDTAV YYCARGYGMDV WGQGTTVTVSS	1701	GYT LTSY G	1702	VSFY NGNT	1703	ARGY GMDV	1704
PCSK9	DIQMTQSPSSL SASVGDRVTIT CRASQGISSAL AWYQQKPGK APKLLIYSASY RYTGVPSRFS GSGSGTDFTFT ISSLQPEDIAT YYCQQRYSL WRTFGQGTKL EIK	1705	QGIS SA	1706	SAS	1707	QQR YSL WRT	1708	QVQLVQSGAEV KKPGASVKVSCK ASGYTFTSYYMH WVRQAPGQGLE WMGEISPFGGRT NYNEKFKSRVTM TRDTSTSTVYME LSSLRSEDTAVY YCARERPLYASD LWGQGTTVTVSS	1709	GYTF TSYY	1710	ISPF GGRT	1711	ARER PLYA SDL	1712
PDGFRA	EIVLTQSPATL SLSPGERATLS CRASQSVSSY LAWYQQKPG QAPRLLIYDAS NRATGIPARFS GSGSGTDFTLT ISSLEPEDFAV YYCQQRSNWP PAFGQGTKVEI K	1713	QSVS SY	1714	DAS	1715	QQRS NWP PA	1716	QLQLQESGPGLV KPSETLSLTCTVS GGSINSSSYYWG WLRQSPGKGLE WIGSFFYTGSTY YNPSLRSRLTISV DTSKNQFSLMLS SVTAADTAVYYC ARQSTYYYGSGN YYGWFDRWDQG TLVTVSS	1717	GGSI NSSS YY	1718	FFYT GST	1719	ARQS TYYY GSGN YYGW FDR	1720

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
PDGFRa	DIQMTQSPSSL SASVGDRVSIT CRPSQSFSRYI NWYQQKPGK APKLLIHAASS LVGGVPSRFS GSGSGTDFTLT ISSLQPEDFAT YYCQQTYSNP PITFGQGTRLE MK	1721	QSFS RY	1722	AAS	1723	QQT YSNP PIT	1724	QVQLVESGGGLV KPGGSLRLSCAA SGFTFSDYYMN WIRQAPGKGLE WVSYISSSGSIIY YADSVKGRFTIS RDNAKNSLYLQ MNSLRAEDTAV YYCAREGRIAAR GMDVWGQGTTV TVSS	1725	GFTF SDY Y	1726	ISSS GSII	1727	AREG RIAA RGMD V	1728
phospha- tidyl- serine	DIQMTQSPSSL SASLGERVSLT CRASQDIGSSL NWLQQGPDG TIKRLIYATSS LDSGVPKRFS GSRSGSDYSLT ISSLESEDFVD YYCLQYVSSP PTFGAGTKLE LK	1729	QDIG SS	1730	ATS	1731	LQY VSSP PT	1732	EVQLQQSGPELE KPGASVKLSCKA SGYSFTGYNMN WVKQSHGKSLE WIGHIDPYYGDT SYNQKFRGKATL TVDKSSSTAYMQ LKSLTSEDSAVY YCVKGGYYGHW YFDVWGAGTTV TVSS	1733	GYSF TGY N	1734	IDPY Y	1735	VKGG GDT	1736 WYFD V	YYGH
polysi- alic acid	DVVMTQTPLS LPVSLGDQASI SCRSSQSLVHS NGNTYLYWY LQKPGQSPKP LIYRVSNRFSG VPDRFSGSGS GTDFTLKISRV EAEDLGVYFC FQGTHVPYTF GGGTRLEIK	1737	QSLV HSNG NTY	1738	RVS	1739	FQGT HVP YT	1740	QIQLQQSGPELV RPGASVKISCKAS GYTFTDYYIHWV KQRPGEGLEWIG WIYPGSGNTKYN EKFKGKATLTVD TSSSTAYMQLSS LTSEDSAVYFCA RGGKFAMDYWG QGTSVTVSS	1741	GYTF TDY Y	1742	IYPG SGNT	1743	ARGG KFAM DY	1744
PSMA	DIVMTQSHKF MSTSVGDRVS IICKASQDVGT AVDWYQQKP GQSPKLLIYW ASTRHTGVPD RFTGSGSGTDF TLTITNVQSED LADYFCQQYN SYPLTFGAGT MLDLK	1745	QDVG TA	1746	WAS	1747	QQY NSYP LTFG AGT M	1748	EVQLQQSGPELV KPGTSVRISCKTS GYTFTEYTIHWV KQSHGKSLEWIG NINPNNGGTTYN QKFEDKATLTVD KSSSTAYMELRS LTSEDSAVYYCA AGWNFDYWGQG TTLTVSS	1749	GYTF TEYT	1750	INPN NGGT	1751	AAGW NFDY	1752

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
PSMA	DIQMTQSPSSL SASVGDRVTIT CKASQNVDTN VAWYQQKPG QAPKSLIYSAS YRYSDVPSRFS GSASGTDFTLT ISSVQSEDFAT YYCQQYDSYP YTFGGGTKLEI K	1753	QNVD TN	1754	SAS	1755	QQY DSYP YT	1756	QVQLVESGGGLV KPGESLRLSCAA SGFTFSDYYMY WVRQAPGKGLE WVAIISDGGYYT YYSDIIKGRFTISR DNAKNSLYLQM NSLKAEDTAVYY CARGFPLLRHGA MDYWGQGTLVT VSS	1757	GFTF SDY Y	1758	ISDG GYYT	1759	ARGF PLLR HGAM DY	1760
PVRL4	DIQMTQSPSSV SASVGDRVTIT CRASQGISGW LAWYQQKPG KAPKFLIYAAS TLQSGVPSRFS GSGSGTDFTLT ISSLQPEDFAT YYCQQANSFP PTFGGGTKVEI K	1761	QGIS GW	1762	AAS	1763	QQA NSFP PT	1764	EVQLVESGGGLV QPGGSLRLSCAA SGFTFSSYNMNW VRQAPGKGLEW VSYISSSSSTIYYA DSVKGRFTISRD NAKNSLSLQMNS LRDEDTAVYYCA RAYYYGMDVW GQGTTVTVSS	1765	GFTF SSYN	1766	ISSS SSTI	1767	ARAY YYGM DV	1768
RGMA	QSALTQPRSVS GSPGQSVTISC TGTSSSVGDSI YVSWYQQHP GKAPKLMLYD VTKRPSGVPD RFSGSKSGNT ASLTISGLQAE DEADYYCYSY AGTDTLFGGG TKVTVL	1769	SSSV GDSI Y	1770	DVT	1771	YSY AGT DTL	1772	EVQLVQSGAEVK KPGASVKVSCKA SGYTFTSHGISW VRQAPGQGLDW MGWISPYSGNTN YAQKLQGRVTM TTDTSTSTAYME LSSLRSEDTAVY YCARVGSGPYYY MDVWGQGTLVT VSS	1773	GYTF TSHG	1774	ISPY SGNT	1775	ARVG SGPY YYMD V	1776
CD240D Blood group D antigen	AIRMTQSPSSF SASTGDRVTIT CRASQDIRNY VAWYQQKSG KAPKFLIYAAS TLQSGVPSRFS GSGSGTDFTLT INSLQSEDFAT YYCQQYYNSP PTFGQGTRVEI T	1777	QDIR NY	1778	AAS	1779	QQY YNSP PT	1780	QVQLVESGGGV VQPGRSLRLSCT ASGFTFKNYAMEI WVRQAPAKGLE WVATISYDGRNI QYADSVKGRFTF SRDNSQDTLYLQ LNSLRPEDTAVY YCARPVRSRWLQ LGLEDAFHIWGQ GTMVTVSS	1781	GFTF KNY A	1782	ISYD GRNI	1783	ARPV RSRW LQLG LEDA FHI	1784

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
root plate-specific spondin 3	DIQMTQSPSSL SASVGDRVTIT CKASQSVDYD GDSYMNWYQ QKPGKAPKLLI YAASNLESGV PSRFSGSGSGT DFTLTISPVQA EDFATYYCQQ SNEDPLTFGA GTKLELK	1785	QSVD YDGD SY	1786	AAS	1787	QQS NEDP LT	1788	QVQLVQSGAEV KKPGASVKVSCK ASGYTFTDYSIH WVRQAPGQGLE WIGYIYPSNGDS GYNQKFKNRVT MTRDTSTSTAYM ELSRLRSEDTAV YYCATYFANNFD YWGQGTTLTVSS	1789	GYTF TDYS	1790	IYPS NGDS	1791	ATYF ANNF DYW	1792
serum amyloid P com-ponent	DIQMTQSPSSL SASVGDRVTIT CRASENIYSYL AWYQQKPGK APKLLIHNAK TLAEGVPSRFS GSGSGTDFTLT ISSLQPEDFAT YYCQHHYGAP LTFGQGTKLEI K	1793	ENIY SY	1794	NAK	1795	QHH YGA PLT	1796	QVQLVQSGAEV KKPGSSVKVSCK ASGFTFATYNMH WVRQAPGQGLE WMGYIYPGDGN ANYNQQFKGRV TITADKSTSTAY MELSSLRSEDTA VYYCARGDFDY DGGYYFDSWGQ GTLVTVSS	1797	GFTF ATY N	1798	IYPG DGNA	1799	ARGD FDYD GGYY FDS	1800
STEAP-1	DIQMTQSPSSL SASVGDRVTIT CKSSQSLLYRS NQKNYLAWY QQKPGKAPKL LIYWASTRES GVPSRFSGSGS GTDFTLTISSL QPEDFATYYC QQYYNYPRTF GQGTKVEIK	1801	QSLL YRSN QKNY	1802	WAS	1803	QQY YNY PRT	1804	EVQLVESGGGLV QPGGSLRLSCAV SGYSITSDYAWN WVRQAPGKGLE WVGYISNSGSTS YNPSLKSRFTISR DTSKNTLYLQMN SLRAEDTAVYYC ARERNYDYDDY YYAMDYWGQGT LVTVSS	1805	GYSI TSDY A	1806	ISNS GST	1807	ARER NYDY DDYY YAMD Y	1808
TACSTD2	DIQLTQSPSSL SASVGDRVSIT CKASQDVSIA VAWYQQKPG KAPKLLIYSAS YRYTGVPDRF SGSGSGTDFTL TISSLQPEDFA VYYCQQHYIT PLTFGAGTKV EIK	1809	QDVS IA	1810	SAS	1811	QQH YITP LT	1812	QVQLQQSGSELK KPGASVKVSCKA SGYTFTNYGMN WVKQAPGQGLK WMGWINTYTGE PTYTDDFKGRFA FSLDTSVSTAYL QISSLKADDTAV YFCARGGFGSSY WYFDVWGQGSL VTVSS	1813	GYTF TNY G	1814	INTY TGEP	1815	ARGG FGSS YWYF DV	1816

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
TGFb	ETVLTQSPGTL SLSPGERATLS CRASQSLGSS YLAWYQQKP GQAPRLLIYG ASSRAPGIPDR FSGSGSGTDFT LTISRLEPEDF AVYYCQQYA DSPITFGQGTR LEIK	1817	QSLG SSY	1818	GAS	1819	QQY ADSP IT	1820	QVQLVQSGAEV KKPGSSVKVSCK ASGYTFSSNVIS WVRQAPGQGLE WMGGVIPIVDIA NYAQRFKGRVTI TADESTSTTYME LSSLRSEDTAVY YCASTLGLVLDA MDYWGQGTLVT VSS	1821	GYTF SSNV	1822	VIPI VDIA	1823	ASTL GLVL DAMD Y	1824
TIGIT	DIVMTQSPDSL AVSLGERATIN CKSSQTVLYSS NNKKYLAWY QQKPGQPPNL LIYWASTRES GVPDRFSGSG SGTDFTLTISS LQAEDVAVYY CQQYYSTPFTF GPGTKVEIK	1825	QTVL YSSN NKKY	1826	WAS	1827	QQY YSTP FT	1828	EVQLQQSGPGLV KPSQTLSLTCAIS GDSVSSNSAAWN WIRQSPSRGLEW LGKTYYRFKWY SDYAVSVKGRITI NPDTSKNQFSLQ LNSVTPEDTAVF YCTRESTTYDLL AGPFDYWGQGT LVTVSS	1829	GDS VSSN SAA	1830	TYYR FKWY S	1831	TRES TTYD LLAG PFDY	1832
TWEAKR	DIQMTQSPSSL SASVGDRVTIT CRASQSVSTSS YSYMHWYQQ KPGKAPKLLIK YASNLESGVP SRFSGSGSGTD FTLTISSLQPE DFATYYCQHS WEIPYTFGGG TKVEIK	1833	QSVS TSSY SY	1834	YAS	1835	QHS WEIP YT	1836	EVQLVESGGGLV QPGGSLRLSCAA SGFTFSSYWMSW VRQAPGKGLEW VAEIRLKSDNYA THYAESVKGRFT ISRDDSKNSLYLQ MNSLRAEDTAV YYCTGYYADAM DYWGQGTLVTV SS	1837	GFTF SSY W	1838	IRLK SDNY AT	1839	TGYY ADAM DY	1840
TYRP1	EIVLTQSPATL SLSPGERATLS CRASQSVSSY LAWYQQKPG QAPRLLIYDAS NRATGIPARFS GSGSGTDFTLT ISSLEPEDFAV YYCQQRSNW LMYTFGQGTK LEIK	1841	QSVS SY	1842	DAS	1843	QQRS NWL MYT	1844	QVQLVQSGSELK KPGASVKISCKA SGYTFTSYAMN WVRQAPGQGLE SMGWINTNTGNP TYAQGFTGRFVF SMDTSVSTAYLQ ISSLKAEDTAIYY CAPRYSSSWYLD YWGQGTLVTVSS	1845	GYTF TSYA	1846	INTN TGNP	1847	APRY SSSW YLDY	1848

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
VEGFR2	DIQMTQSPSSL SASVGDRVTIT CRASQDIAGSL NWLQQKPGK AIKRLIYATSS LDSGVPKRFS GSRSGSDYTL TISSLQPEDFA TYYCLQYGSF PPTFGQGTKV EIK	1849	QDIA GS	1850	ATS	1851	LQY GSFP PT	1852	EVQLVESGGGLV QPGGSLRLSCAA SGFTFSSYGMSW VRQAPGKGLEW VATITSGGSYTY YVDSVKGRFTIS RDNAKNTLYLQ MNSLRAEDTAV YYCVRIGEDALD YWGQGTLVTVSS	1853	GFTF SSYG	1854	ITSG GSYT	1855	VRIG EDAL DY	1856
VEGFR2	DIQMTQSPSSV SASIGDRVTIT CRASQGIDNW LGWYQQKPG KAPKLLIYDAS NLDTGVPSRFS GSGSGTYFTLT ISSLQAEDFAV YFCQQAKAFP PTFGGGTKVDI K	1857	QGID NW	1858	DAS	1859	QQA KAFP PT	1860	EVQLVQSGGGLV KPGGSLRLSCAA SGFTFSSYSMNW VRQAPGKGLEW VSSISSSSSYIYY ADSVKGRFTISR DNAKNSLYLQM NSLRAEDTAVYY CARVTDAFDIWG QGTMVTVSS	1861	GFTF SSYS	1862	ISSS SSYI	1863	ARVT DAFD I	1864
VSIR	DIQMTQSPSSL SASVGDRVTIT CRASQSIDTRL NWYQQKPGK APKLLIYSASS LQSGVPSRFSG SGSGTDFTLTI SSLQPEDFATY YCQQSAYNPI TFGQGTKVEI K	1865	QSID TR	1866	SAS	1867	QQS AYN PIT	1868	QVQLVQSGAEV KKPGSSVKVSCK ASGGTFSSYAIS WVRQAPGQGLE WMGGIIPIFGTAN YAQKFQGRVTIT ADESTSTAYMEL SSLRSEDTAVYY CARSSYGWSYEF DYWGQGTLVTV SS	1869	GGTF SSYA	1870	IIPI FGTA	1871	ARSS YGWS YEFD Y	1872
CD171 (L1CAM)	DIVMSQSPSSL AVSVGEKVTM SCKSSQSLLYS SNQKNYLAW YQQKPGQSPK LLIYWASTRES GVPDRFTGSG SGTDFTLTISS VKAEDLALYY CQQYHSYPFT FGSGTKLEIK	1873	QSLL YSSN QKNY	1874	WAS	1875	QQY HSYP FT	1876	QVQLQQPGDELV KPGASVKLSCKA SGYTFTSYWMQ WVKQRPGQGLE WIGEINPSNGRTN YNEMFKSKATLT VDKSSSTAYMQL SSLTSEDSAVYY CALYDGYYAMD YWGQGTSVTVSS	1877	GYTF TSY W	1878	INPS NGRT	1879	ALYD GYYA MDY	1880

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
CD171 (L1CAM)	DIQMTQSSSSF SVSLGDRVTIT CKANEDINNR LAWYQQTPG NSPRLLISGAT NLVTGVPSRFS GSGSGKDYTL TITSLQAEDFA TYYCQQYWST PFTFGSGTELE IK	1881	EDIN NR	1882	GAT	1883	QQY WSTP FT	1884	QVQLQQPGAELV KPGASVKLSCKA SGYTFTGYWMH WVKQRPGHGLE WIGEINPSNGRTN YNERFKSKATLT VDKSSTTAFMQL SGLTSEDSAVYF CARDYYGTSYNF DYWGQGTTLTV SS	1885	GYTF TGY W	1886	INPS NGRT	1887	ARDY YGTS YNFD Y	1888
CD19	EIVLTQSPAIM SASPGERVTM TCSASSGVNY MHWYQQKPG TSPRRWIYDTS KLASGVPARF SGSGSGTSYSL TISSMEPEDAA TYYCHQRGSY TFGGGTKLEIK	1889	SGVN Y	1890	DTS	1891	HQR GSYT	1892	QVQLVQPGAEV VKPGASVKLSCK TSGYTFTSNWMH WVKQAPGQGLE WIGEIDPSDSYTN YNQNFQGKAKL TVDKSTSTAYME VSSLRSDDTAVY YCARGSNPYYYA MDYWGQGTSVT VSS	1893	GYTF TSN W	1894	IDPS DSYT	1895	ARGS NPYY YAMD Y	1896
CD28	DIQMTQSPSSL SASVGDRVTIT CHASQNIYVW LNWYQQKPG KAPKLLIYKAS NLHTGVPSRFS GSGSGTDFTLT ISSLQPEDFAT YYCQQGQTYP YTFGGGTKVE IK	1897	QNIY VW	1898	KAS	1899	QQG QTYP YT	1900	QVQLVQSGAEV KKPGASVKVSCK ASGYTFTSYYIH WVRQAPGQGLE WIGCIYPGNVNT NYNEKFKDRATL TVDTSISTAYME LSRLRSDDTAVY FCTRSHYGLDWN FDVWGQGTTVT VSS	1901	GYTF TSYY	1902	IYPG NVNT	1903	TRSH YGLD WNFD V	1904
CD4	DIQMTQSPSSL SASLGGKVTIA CKASQDINNYI AWYQHKPGK GPRLLIYHTST LQPGIPSRFSG SGSGRDYSFSI SNLEPEDIATY YCIQYNDLFLT TFGGGTKLEIK	1905	QDIN NY	1906	HTS	1907	IQYN DLFL TT	1908	EVILVESGGAIVE PGGSLKLSCSAS GFTFSNYAMSW VRQTPEKRLEWV AAISDHSTNTYY PDSVKGRFTISRD NAKNTLYLQMN SLRSEDTAIYYCA RKYGGDYDPED YWGQGTTLTVSS	1909	GFTF SNY A	1910	ISDH STNT	1911	ARKY GGDY DPED Y	1912

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
CD47	DVLMTQTPLS LPVSLGDQASI SCRSSQSIVYS NGNTYLGWY LQKPGQSPKL LIYKVSNRFSG VPDRFSGSGS GTDFTLKISRV EAEDLGVYHC FQGSHVPYTF GGGTKVEIK	1913	QSIV YSNG NTY	1914	KVS	1915	FQGS HVP YT	1916	QVQLQQPGAELV KPGASVMMSCK ASGYTFTNYNM HWVKQTPGQGL EWIGTIYPGNDD TSYNQKFKDKAT LTADKSSSAAYM QLSSLTSEDSAV YYCARGGYRAM DYWGQGTSVTV SS	1917	GYTF TNY DYN	1918	IYPG NDDT	1919	ARGG YRAM	1920
CD8	DVQINQSPSFL AASPGETITNC RTSRSISQYLA WYQEKPGKT NKLLIYSGSTL QSGIPSRFSGS GSGTDFTLTIS GLEPEDFAMY YCQQHNENPL TFGAGTKLEL K	1921	RSIS QY	1922	SGS	1923	QQH NENP LT	1924	QVQLQQSGAELV KPGASVKLSCTA SGFNIKDTYIHFV RQRPEQGLEWIG RIDPANDNTLYA SKFQGKATITAD TSSNTAYMHLCS LTSGDTAVYYCG RGYGYYVFDHW GQGTTLTVSS	1925	GFNI KDT Y	1926	IDPA NDNT	1927	GRGY GYYV FDH	1928
KIR2DL 2	EIVLTQSPVTL SLSPGERATLS CRASQSVSSY LAWYQQKPG QAPRLLIYDAS NRATGIPARFS GSGSGTDFTLT ISSLEPEDFAV YYCQQRSNW MYTFGQGTKL EIK	1929	QSVS SY	1930	DAS	1931	QQRS NWM YT	1932	QVQLVQSGAEV KKPGSSVKVSCK ASGGTFSFYAIS WVRQAPGQGLE WMGGFIPIFGAA NYAQKFQGRVTI TADESTSTAYME LSSLRSDDTAVY YCARIPSGSYYY DYDMDVWGQGT TVTVSS	1933	GGTF SFYA	1934	FIPI FGAA	1935	ARIP SGSY YYDY DMDV	1936
pMHC [NY-ESO1]	QSELTQPRSVS GSPGQSVTISC TGTSRDVGGY NYVSWYQQH PGKAPKLIIHD VIERSSGVPDR FSGSKSGNTAS LTISGLQAEDE ADYYCWSFA GSYYVFGTGT DVTVL	1937	SRDV GGYN Y	1938	DVI	1939	WSF AGS YYV	1940	EVQLLESGGGLV QPGGSLRLSCAA SGFTFSTYQMSW VRQAPGKGLEW VSGIVSSGGSTAY ADSVKGRFTISR DNSKNTLYLQM NSLRAEDTAVYY CAGELLPYYGM DVWGQGTTVTV SS	1941	GFTF STYQ	1942	IVSS GGST	1943	AGEL LPYY GMDV	1944

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
pMHC [MART1]	QSVLTQPPSV SGAPGQRVTI SCTGSSSNIG AGYDVHWYQQ LPGTAPKLLI YGNSNRPSGV PDRFSGSKSG TSASLAITGL QAEDEADYYC QSYDNSLSSW VFGGGTKLTV L	1945	SSNIGAGYD	1946	GNS	1947	QSYDNSLSSWV	1948	EVQLQQSGAE VKKPGSSVKV SCKASGGTFS SYAISWVRQA PGQGLEWMGR IIPILGIANY AQKFQGRVTI TADKSTSAYM ELSSLRSEDT AVYYCARDVG SGSYSLDYWG QGTLVTVSS	1949	GGTFSSYA	1950	IIPILGIA	1951	ARDVGSGSYS LDY	1952
pMHC [MAGEA1]	SYVLTQPPSV SVAPGQTARI TCGGNNIGSR SVHWYQQKPG QAPVLVVYDD SDRPSGIPER FSGSNSGNMA TLTISRVEAG DEADYYCQVW DSRTDHWVFG GGTDLTVL	1953	NIGSRS	1954	DDS	1955	QVWDSRTDHW V	1956	EVQLVESGGG LVQPGRSLRL SCAASGFTFD DYAMHWVRQA PGKGLEWVSG ISWNSGSIGY ADSVKGRFTI SRDNAKNSLY LQMNSLRAED TAVYYCARGR GFHYYYYGMD IWGQGTTVTV SS	1957	GFTFDDYA	1958	ISWNSGSI	1959	ARGRGFHYYY YGMDI	1960
pMHC [Tyrosi-nase]	EVILTQSPLS LPVTPGEPAS ISCRSSQSLL HSIGYNYLDW YLQKPGQSPQ LLIYLGSNRA SGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCMQALQTP LTFGGGTKVE IK	1961	QSLLHSIGYN	1962	LGS	1963	MQALQTPLT	1964	EVQLVESGGG VQPGRSLRLS CAASGFTFRS YGMHWVRQAP GKGLEWVAVI SYDGSNKYYT DSVNGRFTIS RDNSKNTLYQ MNSLRAEDTA VYYCARGGGY YETSGPDYWG QGTLVTVSS	1965	GFTFRSYG	1966	ISYDGSNK	1967	ARGGGYYETS GPDY	1968
pMHC [Tyrosi-nase]	DVVMTQSPLS LPVTPGEPAS ISCRSSQSLL HSNGHNYLDW YLQKPGQSQL LIYLGSNRSG VPDRFSGSGS GTDFTLKISR VEAEDVGVYY CMQTLQTPLT FGPGTKVDIK	1969	QSLLHSNGHNY	1970	LGS	1971	MQTLQTPLT	1972	EVQLVETGGG VQPGRSLRLS CAASGFTFSS YGMHWVRQAP GKGLEWVAVI SYDGSNKYYA DSVKGRFTIS RDNSKNTLYL QMNSLRAEDT AVYYCAKDRY GWGSSFGHDY WGQGTLTVSS	1973	GFTFSSYG	1974	ISYDGSNK	1975	AKDRYGWGSS FGHDY	1976

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
pMHC [gp100]	QSVLTQPPSVS AAPGQTVTISC SGSSSNIGRNY VSWFQQVPGR APKLLIYDNN QRPSGIPGRFS ASKSDTSATL DITGLQSGDE AVYYCGTWD STLDLYVFGG GTHVPVL	1977	SSNI GRNY	1978	DNN	1979	GTW DSTL DLY V	1980	EVQLVQSGAEVK KPGASVKVSCKA SGYTFTSYYIHW VRQAPGQGLEW MGAINPSGGSTP YAQKFQGRVTM TRDTSTSTVYME LSSLRSEDTAVY YCARDGTYGSGS YPYYYYYGMDV WGQGTTVTVSS	1981	GYTF TSYY	1982	INPS GGST	1983	ARDG TYGS GSYP YYYY YGMD V	1984
pMHC [MUC1]	ETTLTQSPGTL SLSLSPGERAT LSCRASQSVSS SYLAWYQQKP GQAPRLLIYG ASSRATGIPDR FSGSGSGTDFT LTISRLEPEDF AVYYCQQYGS SPRTFGQQGT KVEIK	1985	ASQS VSS	1986	IYGA	1987	YCQ QYG SSPR T	1988	EVQLVQSGAEVK KPGSSVKVSCKA SGGTFSSYAISW VRQAPGQGLEW MGGIIPIFGTANY AQKFQGRVTITA DESTSTAYMELS SLRSEDTAVYYC ARGPEYCINGVC SLDVWGQGTTV TVSS	1989	GGTF SSYA	1990	IIPI FGTA	1991	ARGP EYCI NGVC SLDV	1992
pMHC [MUC1]	EIVMTQSPATL SLSPGERATLS CRASQSVSSY LAWYQQKPG QAPRLLIYDAS NRATGIPARFS GSGSGTDFTLT ISSLEPEDFAV YYCHQYGSSP QTFGQGTKVE IK	1993	QSVS SY	1994	DAS	1995	HQY GSSP QT	1996	EVQLVQSGAEVK KPGSSVKVSCKA SGGTFSSYAISW VRQAPGQGLEW MGGIIPIFGTANY AQKFQGRVTITA DESTSTAYMELS SLRSEDTAVYYC AVHYGDYVFSS MDVWGQGTTVT VSS	1997	GGTF SSYA	1998	IIPI FGTA	1999	AVHY GDYV FSSM DV	2000
pMHC [tax]	EIVLTQSPATL SLSPGERATLS CRASQSVGSY LAWYQQKPG XAPRLLIYDAS HRATGIPARFS GSGSGTDFTLT ISSLEPEDFAV YYCQQRSNWP PMYTFGQGTK LEIK	2001	QSVG SY	2002	DAS	2003	QQRS NWP PMY T	2004	EVQLVQSGAEVK KPGSSVKVSCKA SGGTFSSYTISWV RQAPGQGLEWM GGIIPIFGTANYA QKFQGRVTITAD KSTSTSTAYMEL SSLRSEDTAVYY CAGDTDSSGYYG AVDYWGQGTLV TVSS	2005	GGTF SSYT	2006	IIPI FGTA	2007	YCAG DTDS SGYY GAVD Y	2008

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
pMHC [gp100]	NFMLTQPHSV SESPGKTVTIS CTGSGGSIDN NYVHWYQQR PGSAPTTVMF EDNQRPSGVP DRFSGSIDSSS NSASLVISGLK TEDEGDYYCQ SSDGSKVVFG GGTKLTVL	2009	GGSI DNNY	2010	EDN	2011	QSSD GSK VV	2012	EVQLVQSGGGV VQPGRSLTLSCA ASGFTFSSYGMH WVRQAPGKGLE WVSVISYDGSNK YYADSVKGRFTI SRDNSKNTLYLM NSLRTEDTAVYY CAKTLSAGEWIG GGAFDIWGHGT MVTVSS	2013	GFTF SSYG	2014	ISYD GSNK	2015	AKTL SAGE WIGG GAFD I	2016
pMHC [NY-ESO1]	DIVMTQSPDSL AVSLGERVTIN CKSSQSLLYTS NNRNYLAWY QLKPGQPPKL LIYWASTRES GVPDRFSGSG SGTDFTLTISG LQAEDVAVYY CQQYYKSPLF GQGTKLEIK	2017	QSLL YTSN NRNY	2018	WAS	2019	QQY YKSP L	2020	QVQLQESGPGLV KPSQTLALTCSVI GGSISSGDYYWS WIRQPPGKGLEW VGYISDSGSTYN EPSLNSRVTISVD TSKNQFSLKLFS MTAADTAVYYC ARVRIQGASWGF FDLWGRGTLVSV SS	2021	GGSI SSGD YY	2022	ISDS GST	2023	ARVR IQGA SWGF FDL	2024
pMHC [NY-ESO1]	EIVMTQSPATL SVSPGERATLS CRASQSFSDD LAWYQQKPG QAPRLLIYAAS TRATGIPARFS GRGSGTEFTLT ISSLQSEDSAV YYCQQYNNW PQTFGQGTKV EIK	2025	QSFS DD	2026	AAS	2027	QQY NNW PQT	2028	QVQLVQSGVEV KKPGASVKVSCK ASGYTFASYGIS WVRQAPGQGLE WMGWISVYNGK TNPAERHLGRVT MTTDTSTNTAY MELRNLKSDDTA VYYCAREGGFY GSGSHYRYFAM DVWGQGTTVIVS S	2029	GYTF ASY G	2030	ISVY NGKT	2031	AREG GFYG SGSH YRYF AMDV	2032
pMHC [NY-ESO1]	DIVMTQTPLSL PVTLGQPASLS CRSSQSLVFTD GNTYLNWFQ QRPGQSPRRLI YKVSSRDPGV PDRFSGTGSGT DFTLEISRVEA EDIGVYYCMQ GTHWPPIFGQ GTKVEIK	2033	QSLV FTDG NTY	2034	KVS	2035	MQG THW PPI	2036	QVQLVQSGGGV VRPGGSLRLSCA ASGFSFIDYGMS WVRQVPGKGLE WVAGMNWSGD KKGHAESVKGRF IISRDNAKNTLYL EMSSLRVEDTAL YFCARGEYSNRF DPRGRGTLVTVS S	2037	GFSF IDYG	2038	MNWS GDKK	2039	ARGE YSNR	2040

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
pMHC [NY-ESO1]	EIVLTQSPGTL SLSPGERATLS CRASQSVSSSY LGWYQQKPG QAPRLLIYGAS IRATGIPDRFS GSGSGTDFTLT ISRLEPDDFAV YYCQHYDNSL ITFGHGTRLDI K	2041	QSVS SSY	2042	GAS	2043	QHY DNSL ITFG HGT R	2044	EVQLQESGPGLV KPSETLSLTCTVS GGSISSDYWTWI RQPAGKGLEWIG RIYPRGTSNYNPS LKSRVTMSVDTS KNQISLRLSSVTA ADTAVYYCARE YYYVTNGYFSPG FDYWGQGTLVT VSS	2045	GGSI SSDY	2046	IYPR GTS	2047	AREY YYVT NGYF SPGF DY	2048
pMHC [NY-ESO1]	DIVMTQSPLSL PVTPGEPASIS CRSSQSLHSN GYNYLDWYL QKPGQSPQLLI YLVSNRASGV PDRFSGTGSGT DFTLKISRVEA EDVGVYYCM QAVQTPFTFG PGTKVDIK	2049	QSLH SNGY NY	2050	LVS	2051	MQA VQTP FT	2052	EVQLVESGGGVV QPGKSLRLSCAA SGFIFSSFAVHWV RQAPGKGLEWV ATISSDGSNEDY VDSVKGRFIISRD NSKNTLYLQMNS LRRDDTAVYYC GTGHSTEYYDGL LGVWGHGTTVS VSS	2053	GFIF SSFA	2054	ISSD GSNE	2055	GTGH STEY YDGL LGV	2056
pMHC [MARTI]	QSVVTQPPSVS AAPGRKVTISC SGSSSNIGSNY VSWYQQVPGT APKLLIYEDD KRPSGIPDRFS GSKGTSATLGI TGLQTGDEAD YFCATWDRTV NVVRFGGGTR LTV	2057	SSNI GSNY	2058	EDD	2059	ATW DRT VNV VR	2060	QLQLQESGPGLV KPSETLSLTCTVS GGSISSSSYYWG WIRQPPGKGLEW GSIYYSGTYYNPS LKSRVTISVDTSK NQFSLKLSSTAA DTAVYYCARHV GHELDYWGQGT LVTVSS	2061	GGSI SSSS YY	2062	IYYS GT	2063	ARHV GHEL DY	2064
pMHC [Tyrosinase]	DVVMTQSPLS LPVTPGEPASI SCRSSQSLLHS IGYNYLHWFL QKGQSPQLLIY LGSNRASGVP DRFSGSGSGT DFTLKISRVEA EDVGVYYCM QALQTPPTFG QGTRLEIK	2065	QSLL HSIG YNY	2066	LGS	2067	MQA LQTP PT	2068	QLQLQESGPGLV KPSGTLSLTCAVS GGSISSSNWWSW VRQPPGKGLEWI GEIYHSGSTNYN PSLKSRVTISDKS KNQFSLKLSSVT AADTAVYYCVG SPYGDYVLDYW GQGTLVTVSS	2069	GGSI SSSN W	2070	IYHS GST	2071	VGSP YGDY VLDY	2072

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
pMHC [WT-1]	QAVVTQPPSA SGTPGQRVTIS CSGSSSNIGSN TVNWYQQVP GTAPKLLIYSN NQRPSGVPDR FSGSKSGTSAS LAISGLQSEDE ADYYCAAWD DSLNGWVFGG GTKLTVL	2073	SSNI GSNT	2074	SNN	2075	AAW DDSL NGW V	2076	QMQLVQSGAEV KEPGESLRISCKG SGYSFTNFWISW VRQMPGKGLEW MGRVDPGYSYST YSPSFQGHVTISA DKSTSTAYLQWN SLKASDTAMYYC ARVQYSGYYDW FDPWGQGTLVTV SS	2077	GYSF TNF W	2078	VDPG YSYS	2079	ARVQ YSGY YDWF DP	2080
pMHC [EBNA-1]	DIVMTQSQKF MSTSVGDRVS ITCKASQNVH TAVAWYQQK AGQSPKALIYL ASNRHTGVPD RFTGSGSGTDF TLTISNVQSED LADYFCLQHW NNPLTFGAGT KLELK	2081	QNVH TA	2082	LAS	2083	LQH WNN PLT	2084	QVQLKESGPGLV APSQSLSITCTVS GFSLTGYGVNW VRQPPGKGLEWL GMIWGDGSTDY NSALKSRLSISKD NSKSQVFLKMNS LQTDDTARYYCA RDPYGYIFDYWG QGTTLTVSS	2085	GFSL TGY G	2086	IWGD GST	2087	ARDP YGYI FDY	2088
pMHC [LMP2]	DIVMTQSQKF MSTSVGDRVS VTCRASQNVF TNVAWYQQK PGQAPKALIYS TSYRYSGVPD RFTGSGSGTDF TLTISNVQSED LAEYFCQQYIS YPLTFGAGTK LELK	2089	QNVF TN	2090	STS	2091	QQYI SYPL T	2092	QVQLKQSGPGLV QPSQSLSITCTVS GFSLTNYGVHW VRQSPGKGLEwl GVIWSGGSTDYN AAFISRLSISKDN SKQVFFKMNSLQ ANDTAIYYCARN WVPYYFDYWGQ GTTLTVSS	2093	GFSL TNY G	2094	IWSG GST	2095	ARNW VPYY FDY	2096
pMHC [gp100]	ETTLTQSPGTL SLSPGERATLS CRASQSVSSN YLAWYQQKP GQAPRLLIYA ASSRATGIPDR FSGSGSGTDFT LTISRLEPEDF AVYYCQQYGS SRSFGQGTKL EIK	2097	QSVS SNY	2098	AAS	2099	QQY GSSR S	2100	QVQLQESGGGLV KPGGSLRLSCAA SGFTFSSYSMNW VRQAPGKGLEW VSYISSSGSTIYY ADSVRGRFTISRD NAKNTLYLQMN SLRAEDTAVYYC VRGDPYFFYYYG MDIWGQGTTVT VSS	2101	GFTF SSYS	2102	ISSS GSTI	2103	VRGD PYFF YYYG MDI	2104

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
pMHC [gp100]	DIQLTQSPSSL SASVGDRVIIT CRATQSISTHL NWYQQKPGK APKLLIYSASS LQSGVPSRFSG SGSGSTDFTLT ISSLQPEDFAT YYCQQSYSSP PITFGQGTRLE IK	2105	QSIS TH	2106	SAS	2107	QQS YSSP PIT	2108	QVQLQESGPGLV KPSETLSLTCTVS GGSISSNMYYWG WVRQPPGKGLE WIGSIDYSGSTYY NPSLRSRVTMSV DTSKKQFSLKMT SVTAADTAVYYC ARESGSPYYFDY WGQGTLVTVSS	2109	GGSI SSN MYY	2110	IDYS GST	2111	ARES GSPY YFDY	2112
pMHC [hTERT]	ETTLTQSPGTL SLSPGERATLS CRASQSVSSSY LAWYQQKPG QAPRLLIYGAS TRATGVPDRF SGSGSGTDFTL ISRLEPEDFAV YYCQQYGTSL TWYFGQGTK VEIK	2113	QSVS SSY	2114	GAS	2115	QQY GTSL TWY	2116	QVQLQESGPGLV KPSETLSLTCTVS GGSISSSSYYWA WIRQPPGKLEWI GEWINHSGSTNY NPSLKSRVTISVD TSKNQFSLNLNS VTAADTAVYYC ARVVAAAGHYY YYYMDVWGKGT TVTVSS	2117	GGSI SSSS YY	2118	WINH SGST	2119	ARVV AAAG HYYY YYMD V	2120
pMHC [hTERT]	ETTLTQSPGTL SLSPGERATLS CRASQSVSSR YLAWYQQKP GQAPRLLIYG ASSRATGIPDR FSGSGSGTDFT LTISRLEPEDF AVYYCQQYGS SNTFGQGTKL EIK	2121	QSVS SRY	2122	GAS	2123	QQY GSSN T	2124	QVQLQESGPGLV KPSETLSLTCTVS GGSISSSYYWGW IRQPPGKGLEWIG SIYYSGSTYYNPS LKSRVTISVDTSK NQFSLKLSSVTA ADTAVYYCARSR SGSYLNDAFDIW GQGTMVTVSS	2125	GGSI SSSY Y	2126	IYYS GST	2127	ARSR SGSY LNDA FDI	2128
pMHC [hTERT]	ETTLTQSPGTL SLSPGERATLS CRASQSVSSSY LAWYQQKPG QAPRLLIYGAS SRATGIPDRFS GSGSGTDFTLT ISRLEPEDFAV YYCQQYGSSS GTFGQGTKVE IK	2129	QSVS SSY	2130	GAS	2131	QQY GSSS GT	2132	QVQLQQSGAEV KKPGSSVKVSCK ASGGTFSSYAIS WVRQAPGQGLE WMGRIIPILGIAN YAQKFQGRVTIT ADKSTSTAYMEL SSLRSEDTAVYY CARGFRPYYYYG MDVWGQGTTVT VSS	2133	GGTF SSYA	2134	IIPI LGIA	2135	ARGF RPYY YYGM DV	2136

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
pMHC [gp100]	QSVVTQPPSVS GAPGQRVTISC TGSSSNIGAGY DVHWYQQLP GTAPKLLIYG NSNRPSGVPD RFSGSKSGTSA SLAITGLQAED EADYYCQSYD SSLSALFGGGT KLTVL	2137	SSNI GAGY D	2138	GNS	2139	QSY DSSL SAL	2140	QVQLQQSGPGLV KPSETLSLTCTVS GGSIRNYYWSWI RQPPGKGLEWIG YMYYSGGANYN PSLNSRVTISLDT SKNQFSLKLTSV TAADTAVYYCA RIPNYYDRSGYY PGYWYFDLWGR GTLVTVSS	2141	GGSI RNY Y	2142	MYYS GGA	2143	ARIP NYYD RSGY YPGY WYFD L	2144
pMHC [gp100]	DIQLTQSPSSL SASVGDRVTIT CRASQSISTYL NWYQHRPGK APKLLIYSASS LQSGVPSRFSG SGSGTDFTLTI SSLQPEDFATY YCQQSDIIPLT FGGGTKVEIN	2145	QSIS TY	2146	SAS	2147	QQS DIIP LT	2148	QVQLQQSGPGLV KPSQTLSLTCAIS GDSISSNSVVWN WIRQSPSRGLEW LGRTYYRSKWY NDYAVSVKSRITI NPDTSKNQFSLQ LNSVTPDDTALY YCARASFGTSGK FDDWGQGTLVT VSS	2149	GDSI SSNS VV	2150	TYYR SKWY N	2151	ARAS FGTS GKFD D	2152
pMHC [hTERT]	SYVLTQPPSVS EAPGKTARITC EGITIGRKSVH WYQQKPGQA PVLVVYDDTV RPSGVPERFSG SNSGNTATLII SGVEAGDEAD YCQVWDSSTD PQVVFGGGTK TVL	2153	TIGR KS	2154	DDT	2155	QVW DSST DPQ VV	2156	QVQLQQSGPGLV KPSQTLSLTCAIS GDSVSSKNSSWN WIRQSPSRGLEW LGRTYYRSKWY YDYAVSVKGRIT FTFPDTSKNQVSL HLNAVTPEDTAM YYCVRGSIFDVW GQGTMVTVSS	2157	GDS VSSK NSS	2158	TYYR SKWY Y	2159	CVRG SIFD V	2160
pMHC [hTERT]	NFMLTQPHSV SESPGKTVTIS CTGSGGSIATN YVQWYQQRP GSAPATVIYED DQRPSGVPDR FSGSIDSSSNS ASLTISGLKTE DEADYYCQSY DSSNQVFGGG TKLTVL	2161	GGSI ATNY	2162	EDD	2163	QSY DSSN QV	2164	QVQLQQWGAGL LKPSETLSLTCAV YGGSFSGYYWS WIRQPPGKGLEW IGEINHSGSTNYN PSLKSRVTISVDT SKNQFSLKLSSVT AADTAVYYCAR MVRYYYGMDV WGQGTTVTVSS	2165	GGSF SGY Y	2166	INHS GST	2167	ARMV RYYY GMDV	2168

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
pMHC [hTERT]	ETTLTQSPGTL SLSPGERATLS CRASQSVGSN LAWYQQRPG QAPSLLIYGAS SRATGVPDRF SGSGSGTDFTL TISRLEPEDFA VYYCQQYGDS PRLYTFGQGT KLEIK	2169	QSVG SN	2170	GAS	2171	QQY GDSP RLYT	2172	QVQLQQWGAGL LKPSETLSLTCAV YGGSFSGYYWS WIRQPPGKGLEW IGEINHSGSTNYN PSLKSRVTISVDT SKNQFSLKLSSVT AADTAVYYCAR VAYYDSSGYYPY DAFDIWGQGTM VTVSS	2173	GGSF SGY Y	2174	INHS GST	2175	ARVA YYDS SGYY PYDA FDI	2176
pMHC [gp100]	DVVMTQSPGT LSVSPGDSATL SCWASQLSDS YVSWYQQKP GQAPRLLIHSA SIRAP- GIPDRFS GSVSGTEFTLT ISGLEPEDFAV YSCHQYGFLP WTFGQGTKVE IR	2177	QLSD SY	2178	SAS	2179	HQY GFLP WT	2180	QVQLVQSGAEV KKPGASVKVSCK ASGYTFTRYGIS WVRQAPGQGLE WMGWISSSNGY TKYAQNLQGRLT LTTDTSTGTAYM ELRSLRSEDTAL YYCARYDISGLD GFDIWGQGTMV TVSS	2181	GYTF TRY G	2182	ISSS NGYT	2183	ARYD ISGL DGFD I	2184
pMHC [gp100]	ETTLTQSPGTL SLSPGERATLS CRASRYINAN FLAWYQQKPG QAPRLLIYDAS TRATGIPDRFS GSGSGTDFTLT ISRLEPEDFAV YYCQQYGSSP RTFGQGTKVEI K	2185	RYIN ANF	2186	DAS	2187	QQY GSSP RT	2188	QVQLVQSGAEV KKPGSSVKVSCK ASGGTFSSYAIS WVRQAPGQGLE WMGGIIPIFGTAT NYAQKFQGRVTI TADESTSTAYME LSSLRSEDTAVY YCARDSSGWLY DAFDIWGQGTM VTVSS	2189	GGTF SSYA	2190	IIPI FGTA	2191	CARD SSGW LYDA FDI	2192
pMHC [hTERT]	DIQMTQSPSIL SASVGDRVTIT CRASQRFGDY LAWYQQKPG QAPKLLIYGAS TLQSGVPSRFS GSGSGTEFTLT ISGLQPEDFAT YYCQQANSFPI TFGKGTRLDIR	2193	QRFG DY	2194	GAS	2195	QQA NSFP ITFG KGT R	2196	QVQLVQSGAEV KKPGSSVKVSCK ASGGTFSSYAIS WVRQAPGQGLE WMGWINVGNGN AIYSQKFQGRVTI TRDTSATTAYME LSSLRSEDTAVY YCARDGERAWD LDYWGQGTLVT VSS	2197	GGTF SSYA	2198	INVG NGNA	2199	ARDG ERAW DLDY	2200

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
pMHC [hTERT]	ETTLTQSPGTL SLSPGERATLS CRASQSVSSSY LAWYQQKPG QAPRLLIYGAS SRATGIPDRFS GSGSGTDFTLT ISRLEPEDFAV YYCQQYGSSP YTFGQGTKLEI K	2201	QSVS SSY	2202	GAS	2203	QQY GSSP YT	2204	QVQLVQSGGGV VQPGRSLRLSCA ASGFTFSSYAMH WVRQAPGKGLE WVAVISYDGSNK YYADSVKGRFTI SRDNSKNTLYLQ MNSLRAEDTAV YYCARELRFLEW SSDAFDIWGQGT MVTVSS	2205	GFTF SSYA	2206	ISYD GSNK	2207	AREL RFLE WSSD AFDI	2208
pMHC [gp100]	ETTLTQSPGTL SLSPGERATLS CRASQSVSSSY LAWYQQKPG QAPRLLIYGAS SRATGIPDRFS GSGSGTDFTLT ISRLEPEDFAV YYCQQHDSSP RTFGQGTKVEI K	2209	QSVS SSY	2210	GAS	2211	QQH DSSP RT	2212	QVQLVQSGGGV VQPGRSLRLSCA ASGFTFSSYGMH WVRQAPGKGLE WVAFISYDGSDK NFADSVKGRFTIS RDNSKNTLYLQ MNSLRAEDTAV YYCAKDSYYDN SAFQADWGQGT LVTVSS	2213	GFTF SSYG	2214	ISYD GSDK	2215	AKDS YYDN SAFQ AD	2216
pMHC [tax]	EIVLTQSPLSL PVTPGEPASIS CRSSQSLLHSN GYNYLDWYL QKPGQSPQLLI YLGSNRASGV PDRFSGSGSGT DFTLKISRVEA EDVGVYYCM QALQTPRTFG QGTKVEIK	2217	QSLL HSNG YNY	2218	LGS	2219	MQA LQTP RT	2220	QVQLVQSGGGV VQPGRSLRLSCA ASGFTFSSYGMH WVRQAPGKGLE WVAVISYDGSNK YYADSVKGRFTI SRDNSKNTLYLQ MNSLRAEDTAV YYCARDFDYGDS YYYYGMDVWG QGTTVTVSS	2221	GFTF SSYG	2222	ISYD GSNK	2223	ARDF DYGD SYYY YGMD V	2224
pMHC [gp100]	DVMTQSPLSL PVTPGEPASIS CRSSQSLLHSN GYKYVNWYL QKPGQSPQLLI YFGSYRASGV PDRFSGSGSGT DFTLKISRVEA EDVGIYYCMQ ATHWPYTFGQ GTRLEIK	2225	QSLL HSNG YKY	2226	FGS	2227	MQA THW PYT	2228	QVQLVQSGGGV VQPGRSLRLSCA ASGFTFSSYGMH WVRQAPGKGLE WVAVISYDGSNK YYADSVKGRFTI SRDNSKNTLYLQ MNSLRAEDTAV YYCARDYYGDY ALLDYWGQGTL VTVSS	2229	GFTF SSYG	2230	ISYD GSNK	2231	ARDY YGDY ALLD Y	2232

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
pMHC [gp100]	EIVLTQSPDTL SLSPGEREATL SCRASQSVSHS YLAQYQQKPG QAPRLLIYDTS SRATDIPDRFS GSGSGTDFTLT ISRLEPEDSAV YYCQQYVSSP LTFGQGTKLEI K	2233	SQSV SHS	2234	YDT	2235	CQQ YVSS PLT	2236	QVQLVQSGGGV VQPGRSLRLSCA ASGFTFSTYGLH WVRQAPGKGLE WVAFISYDGSNK YYADSVKGRFTI SRDNSKNTLYLQ MNGLRAEDTAV YYCAKTVGVTFV SDAFDIWGQGTM VTVSS	2237	GFTF STYG	2238	ISYD GSNK	2239	AKTV GVTF VSDA FDI	2240
pMHC [NY-ESO1]	QSELTQPRSVS GSPGQSVTISC TGTSRDVGGY NYVSWYQQH PGKAPKLIIHD VIIRPSGVPDR FSGSKSGNTAS LTISGLQAEDE AHYYCWSFA GSYYVFGTGT DVTVL	2241	SRDV GGYN Y	2242	DVI	2243	WSF AGS YYV	2244	QVQLLESGGGLV QPGGSLRLSCAA SGFTFSAYGMG WVRQAPGKGLE WVSSIGSSGGGT AYADSVKGRFTI SRDNSKNTLYLQ MNSLRAEDTAV YYCAGELLPYYG MDVWGQGTTVT VSS	2245	GFTF SAY G	2246	IGSS GGGT	2247	AGEL LPYY GMDV	2248
GD2	ENVLTQSPAI MSASPGEKVT MTCRASSSVS SSLYHWYQQK SGASPKVWIY STSNLASGVP GRFSGSGSGTS YSLTISSVEAE DAATYYCQQ YSGYPITFGAG TKVEVK	2249	SSVS SSL	2250	STS	2251	QQY SGYP IT	2252	QVQLKESGPVLV APSQTLSITCTVS GFSLASYNIHWV RQPPGKGLEWLG VIWAGGSTNYNS ALMSRLSISKDNS KSQVFLQMNSLQ TDDTAMYYCAK RSDDYSWFAYW GCQTLVTVSA	2253	GFSL ASY N	2254	IWAG GST	2255	AKRS DDYS WFAY	2256
STEAP_1	DIVMSQSPSSL AVSVGEKVTM SCKSSQSLLYR SNQKNYLAW YQQKPGQSPK LLIYWASTRES GVPDRFTGSG SGTDFTLTISS VKAEDLAVYY CQQYYNYPRT FGGGTKLEIK	2257	QSLL YRSN QKNY	2258	WAS	2259	QQY YNY PRT	2260	DVQVQESGPGLV KPSQSLSLTCTVT GYSITSDYAWN WIRQFPGNKLEW MGYISNSGSTSY NPSLKSRISITRDT SKNQFFLQLISVT TEDTATYYCARE RNYDYDDYYYA MDYWGQGTTLT VSA	2261	GYSI TSDY A	2262	ISNS GST	2263	ARER NYDY DDYY YAMD Y	2264

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
a4b7	DIQMTQSPSSV	2265	QGIS	2266	GAS	2267	QQA	2268	QVQLVQSGAEV	2269	GYT	2270	FDPQ	2271	ATGS	2272
	SASVGDRVTIT		SW				NSFP		KKPGASVKVSCK		LSDL		DGET		SSSW	
	CRASQGISSW						WT		VSGYTLSDLSIH		S				FDP	
	LAWYQQKPG								WVRQAPGKGLE							
	KAPKLLIYGAS								WMGGFDPQDGE							
	NLESGVPSRFS								TIYAQKFQGRVT							
	GSGSGTDFTLT								MTEDTSTDTAY							
	ISSLQPEDFAN								MELSSLKSEDTA							
	YYCQQANSFP								VYYCATGSSSSW							
	WTFGQGTKVE								FDPWGQGTLVTV							
	IK								SS							
GPC3	DVVMTQSPLS	2273	QSLV	2274	KVS	2275	SQNT	2276	QVQLVQSGAEV	2277	GYTF	2278	LDPK	2279	TRFY	2280
	LPVTPGEPASI		HSNR				HVPP		KKPGASVKVSCK		TDY		TGDT		SYTY	
	SCRSSQSLVHS		NTY				T		ASGYTFTDYEMH		E				W	
	NRNTYLHWY								WVRQAPGQGLE							
	LQKPGQSPQL								WMGALDPKTGD							
	LIYKVSNRFSG								TAYSQKFKGRVT							
	VPDRFSGSGS								LTADKSTSTAYM							
	GTDFTLKISRV								ELSSLTSEDTAVY							
	EAEDVGVYYC								YCTRFYSYTYWG							
	SQNTHVPPTF								QGTLVTVSS							
	GQGTKLEIK															
CD262 (DR5)	SELTQDPAVS	2281	SLRS	2282	GAN	2283	NSA	2284	EVQLVQSGGGVE	2285	GFTF	2286	INWQ	2287	AKIL	2288
	VALGQTVRIT		YY				DSSG		RPGGSLRLSCAA		DDY		GGST		GAGR	
	CSGDSLRSYY						NHV		SGFTFDDYAMS		A				GWYF	
	ASWYQQKPG						V		WVRQAPGKGLE						DY	
	QAPVLVIYGA								WVSGINWQGGS							
	NNRPSGIPDRF								TGYADSVKGRVT							
	SGSSSGNTASL								ISRDNAKNSLYL							
	TITGAQAEDE								QMNSLRAEDTA							
	ADYYCNSADS								VYYCAKILGAGR							
	SGNHVVFGGG								GWYFDYWGKGT							
	TKLTVL								TVTVSS							
CD80	ESALITQPPSVS	2289	TSNI	2290	DIN	2291	QSY	2292	QVQLQESGPGLV	2293	GGSI	2294	FYSS	2295	VRDR	2296
	GAPGQKVTIS		GGYD				DSSL		KPSETLSLTCAVS		SGG		SGNT		LFSV	
	CTGSTSNIGGY						NAQ		GGSISGGYGWG		YG				VGMV	
	DLHWYQQLP						VFG		WIRQPPGKGLEW						YNNW	
	GTAPKLLIYDI						G		IGSFYSSSGNTYY						FDVW	
	NKRPSGISDRF								NPSLKSQVTISTD							
	SGSKSGTAAS								TSKNQFSLKLNS							
	LAITGLQTEDE								MTAADTAVYYC							
	ADYYCQSYDS								VRDRLFSVVGM							
	SLNAQVFGGG								VYNNWFDVWGP							
	TRLTVL								GVLVTVSS							

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
CD22	DVQVTQSPSS LSASVGDRVTI TCRSSQSLANS YGNTFLSWYL HKPGKAPQLLI YGISNRFSGVP DRFSGSGSGT DFTLTISSLQP EDFATYYCLQ GTHQPYTFGQ GTKVEIK	2297	QSLA NSYG NTF	2298	GIS	2299	LQGT HQP YT	2300	EVQLVQSGAEVK KPGASVKVSCKA SGYRFTNYWIHW VRQAPGQGLEWI GGINPGNNYATY RRKFQGRVTMT ADTSTSTVYMEL SSLRSEDTAVYY CTREGYGNYGA WFAYWGQGTLV TVSS	2301	GYR FTNY W	2302	INPG NNYA	2303	TREG YGNY GAWF AY	2304
CD23	DIQMTQSPSSL SASVGDRVTIT CRASQDIRYY LNWYQQKPG KAPKLLIYVAS SLQSGVPSRFS GSGSGTEFTLT VSSLQPEDFAT YYCLQVYSTP RTFGQGTKVEI K	2305	QDIR YY	2306	VAS	2307	LQV YSTP RT	2308	EVQLVESGGGLA KPGGSLRLSCAA SGFRFTFNNYYM DWVRQAPGQGL EWVSRISSSGDPT WYADSVKGRFTI SRENANNTLFLQ MNSLRAEDTAV YYCASLTTGSDS WGQGVLVTVSS	2309	GFRF TFNN YY	2310	ISSS GDPT	2311	ASLT TGSD SW	2312
CD20	DIQMTQSPSSL SASVGDRVTIT CRASSSVSYM HWYQQKPGK APKPLIYAPSN LASGVPSRFSG SGSGTDFTLTI SSLQPEDFATY YCQQWSFNPP TFGQGTKVEI K	2313	SSVS Y	2314	APS	2315	QQW SFNP PT	2316	EVQLVESGGGLV QPGGSLRLSCAA SGYTFTSYNMH WVRQAPGKGLE WVGAIYPGNGDT SYNQKFKGRFTIS VDKSKNTLYLQ MNSLRAEDTAV YYCARVVYYSNS YWYFDVWGQGT LVTVSS	2317	GYTF TSYN	2318	IYPG NGDT	2319	ARVV YYSN SYWY FDV	2320
CD37	EIVLTQSPATL SLSPGERATLS CRASENVYSY LAWYQQKPG QAPRLLIYFAK TLAEGIPARFS GSGSGTDFTLT ISSLEPEDFAV YYCQHHSDNP WTFGQGTKVE IK	2321	ENVY SY	2322	FAK	2323	QHH SDNP WT	2324	EVQLVQSGAEVK KPGESLKISCKGS GYSFTGYNMNW VRQMPGKGLEW MGNIDPYYGGTT YNRKFKGQVTIS ADKSISTAYLQW SSLKASDTAMYY CARSVGPFDSWG QGTLVTVSS	2325	GYSF TGY N	2326	IDPY YGGT	2327	ARSV GPFD S	2328

TABLE 1-continued

Antigen	V_L	SEQ ID NO	V_L CDR1	SEQ ID NO	V_L CDR2	SEQ ID NO	V_L CDR3	SEQ ID NO	V_H	SEQ ID NO	V_H CDR1	SEQ ID NO	V_H CDR2	SEQ ID NO	V_H CDR3	SEQ ID NO
CD22	DIQMTQSPSSL SASVGDRVTIT CRSSQSIVHSV GNTFLEWYQQ KPGKAPKLLIY KVSNRFSGVP SRFSGSGSGTD FTLTISSLQPE DFATYYCFQG SQFPYTFGQG TKVEIK	2329	QSIV HSVG NTF	2330	KVS	2331	FQGS QFPY T	2332	EVQLVESGGGLV QPGGSLRLSCAA SGYEFSRSWMN WVRQAPGKGLE WVGRIYPGDGDT NYSGKFKGRFTIS ADTSKNTAYLQ MNSLRAEDTAV YYCARDGSSWD WYFDVWGQGTL VTVSS	2333	GYEF SRS W	2334	IYPGD GDT	2335	ARDGS SWDW YFDV	2336
fibro-nectin extra domain-B	EIVLTQSPGTL SLSPGERATLS CRASQSVSSSF LAWYQQKPG QAPRLLIYYAS SRATGIPDRFS GSGSGTDFTLT ISRLEPEDFAV YYCQQTGRIPP TFGQGTKVEI K	2337	QSVS SSF	2338	YAS	2339	QQT GRIP PT	2340	EVQLLESGGGLV QPGGSLRLSCAA SGFTFSSFSMSW VRQAPGKGLEW VSSISGSSGTTYY ADSVKGRFTISR DNSKNTLYLQM NSLRAEDTAVYY CAKPFPYFDYWG QGTLVTVSS	2341	GFTF SSFS	2342	ISGS SGTT	2343	AKPF PYFD Y	2344
CD3	DIQMTQSPSSL SASVGDRVTIT CSASSSVSYM NWYQQKPGK APKRLIYDTSK LASGVPSRFSG SGSGTDFTLTI SSLQPEDFATY YCQQWSSNPP TFGGGTKVEI K	2345	SSVS Y	2346	DTS	2347	QQW SSNP PT	2348	QVQLVQSGAEV KKPGASVKVSCK ASGYTFISYTMH WVRQAPGQGLE WMGYINPRSGYT HYNQKLKDKAT LTADKSASTAYM ELSSLRSEDTAV YYCARSAYYDY DGFAYWGQGTL VTVSS	2349	GYTF ISYT	2350	INPR SGYT	2351	ARSAY YDYDG FAY	2352

*Italics means immune cell target/payload (scFv arm)

[0127] In one aspect, the present disclosure provides a heterodimeric multispecific antibody comprising a first polypeptide chain, a second polypeptide chain, a third polypeptide chain and a fourth polypeptide chain, wherein the first and second polypeptide chains are covalently bonded to one another, the second and third polypeptide chains are covalently bonded to one another, and the third and fourth polypeptide chain, and wherein: (a) the first polypeptide chain comprises in the N-terminal to C-terminal direction: (i) a light chain variable domain of a first immunoglobulin (VL-1) that is capable of specifically binding to a first epitope; (ii) a light chain constant domain of the first immunoglobulin (CL-1); (iii) a flexible peptide linker comprising the amino acid sequence $(GGGGS)_3$ (SEQ ID NO: 2506); and (iv) a light chain variable domain of a second immunoglobulin (VL-2) that is linked to a complementary heavy chain variable domain of the second immunoglobulin (VH-2), or a heavy chain variable domain of a second immunoglobulin (VH-2) that is linked to a complementary light chain variable domain of the second immunoglobulin (VL-2), wherein VL-2 and VH-2 are capable of specifically binding to a second epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ (SEQ ID NO: 2507) to form a single-chain variable fragment; (b) the second polypeptide comprises in the N-terminal to C-terminal direction: (i) a heavy chain variable domain of the first immunoglobulin (VH-1) that is capable of specifically binding to the first epitope; (ii) a first CH1 domain of the first immunoglobulin (CH1-1); and (iii) a first heterodimerization domain of the first immunoglobulin, wherein the first heterodimerization domain is incapable of forming a stable homodimer with another first heterodimerization domain; (c) the third polypeptide comprises in the N-terminal to C-terminal direction: (i) a heavy chain variable domain of a third immunoglobulin (VH-3) that is capable of specifically binding to a third epitope; (ii) a second CH1 domain of the third immunoglobulin (CH1-3); and (iii) a second heterodimerization domain of the third immunoglobulin, wherein the second heterodimerization domain comprises an amino acid sequence or a nucleic acid sequence that is distinct from the first heterodimerization domain of the first immunoglobulin, wherein the second heterodimerization domain is incapable of forming a stable homodimer with another second heterodimerization domain, and wherein the second heterodimerization domain of the third immunoglobulin is configured to form a heterodimer with the first heterodimerization domain of the first immunoglobulin; (d) the fourth polypeptide comprises in the N-terminal to C-terminal direction: (i) a light chain variable domain of the third immunoglobulin (VL-3) that is capable of specifically binding to the third epitope; (ii) a light chain constant domain of the third immunoglobulin (CL-3); (iii) a flexible peptide linker comprising the amino acid sequence $(GGGGS)_3$ (SEQ ID NO: 2506); and (iv) a light chain variable domain of a fourth immunoglobulin (VL-4) that is linked to a complementary heavy chain variable domain of the fourth immunoglobulin (VH-4), or a heavy chain variable domain of a fourth immunoglobulin (VH-4) that is linked to a complementary light chain variable domain of the fourth immunoglobulin (VL-4), wherein VL-4 and VH-4 are capable of specifically binding to the second epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ (SEQ ID NO: 2507) to form a single-chain variable fragment, and wherein each of VL-1 and VL-3 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_L amino acid sequence selected from any one of SEQ ID NOs: 1, 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 105, 113, 121, 129, 145, 153, 161, 169, 177, 193, 201, 233, 241, 257, 273, 281, 289, 297, 305, 313, 321, 329, 337, 345, 353, 361, 369, 377, 385, 393, 401, 409, 417, 425, 433, 441, 449, 457, 465, 481, 489, 497, 521, 529, 537, 545, 553, 561, 609, 617, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 777, 785, 793, 801, 809, 817, 825, 833, 841, 849, 857, 865, 873, 881, 889, 945, 953, 961, 977, 985, 993, 1001, 1009, 1017, 1025, 1033, 1041, 1049, 1065, 1073, 1081, 1089, 1097, 1105, 1113, 1121, 1129, 1137, 1145, 1153, 1161, 1169, 1177, 1185, 1193, 1201, 1209, 1217, 1225, 1233, 1241, 1249, 1257, 1265, 1273, 1281, 1289, 1297, 1305, 1313, 1321, 1329, 1337, 1345, 1353, 1361, 1369, 1377, 1385, 1393, 1401, 1409, 1417, 1425, 1433, 1441, 1449, 1457, 1465, 1473, 1481, 1489, 1497, 1505, 1513, 1521, 1529, 1545, 1553, 1561, 1569, 1577, 1585, 1593, 1601, 1609, 1617, 1625, 1633, 1649, 1657, 1673, 1681, 1689, 1697, 1705, 1713, 1721, 1729, 1737, 1745, 1753, 1761, 1769, 1777, 1785, 1793, 1801, 1809, 1817, 1833, 1841, 1849, 1857, 1865, 1873, 1881, 1889, 1913, 1937, 1945, 1953, 1961, 1969, 1977, 1985, 1993, 2001, 2009, 2017, 2025, 2033, 2041, 2049, 2057, 2065, 2073, 2081, 2089, 2097, 2105, 2113, 2121, 2129, 2137, 2145, 2153, 2161, 2169, 2177, 2185, 2193, 2201, 2209, 2217, 2225, 2233, 2241, 2249, 2257, 2265, 2273, 2281, 2297, 2305, 2313, 2321, 2329, 2337 and 2345; and/or wherein each of VH-1 and VH-3 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_H amino acid sequence selected from any one of SEQ ID NOs: 5, 13, 21, 29, 37, 45, 53, 61, 69, 77, 85, 93, 101, 109, 117, 125, 133, 149, 157, 165, 173, 181, 197, 205, 237, 245, 261, 277, 285, 293, 301, 309, 317, 325, 333, 341, 349, 357, 365, 373, 381, 389, 397, 405, 413, 421, 429, 437, 445, 453, 461, 469, 485, 493, 501, 525, 533, 541, 549, 557, 565, 613, 621, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 781, 789, 797, 805, 813, 821, 829, 837, 845, 853, 861, 869, 877, 885, 893, 949, 957, 965, 981, 989, 997, 1005, 1013, 1021, 1029, 1037, 1045, 1053, 1069, 1077, 1085, 1093, 1101, 1109, 1117, 1125, 1133, 1141, 1149, 1157, 1165, 1173, 1181, 1189, 1197, 1205, 1213, 1221, 1229, 1237, 1245, 1253, 1261, 1269, 1277, 1285, 1293, 1301, 1309, 1317, 1325, 1333, 1341, 1349, 1357, 1365, 1373, 1381, 1389, 1397, 1405, 1413, 1421, 1429, 1437, 1445, 1453, 1461, 1469, 1477, 1485, 1493, 1501, 1509, 1517, 1525, 1533, 1549, 1557, 1565, 1573, 1581, 1589, 1597, 1605, 1613, 1621, 1629, 1637, 1653, 1661, 1677, 1685, 1693, 1701, 1709, 1717, 1725, 1733, 1741, 1749, 1757, 1765, 1773, 1781, 1789, 1797, 1805, 1813, 1821, 1837, 1845, 1853, 1861, 1869, 1877, 1885, 1893, 1917, 1941, 1949, 1957, 1965, 1973, 1981, 1989, 1997, 2005, 2013, 2021, 2029, 2037, 2045, 2053, 2061, 2069, 2077, 2085, 2093, 2101, 2109, 2117, 2125, 2133, 2141, 2149, 2157, 2165, 2173, 2181, 2189, 2197, 2205, 2213, 2221, 2229, 2237, 2245, 2253, 2261, 2269, 2277, 2285, 2301, 2309, 2317, 2325, 2333, 2341, and 2349.

[0128] In one aspect, the present disclosure provides a heterodimeric multispecific antibody comprising a first polypeptide chain, a second polypeptide chain, a third polypeptide chain and a fourth polypeptide chain, wherein the first and second polypeptide chains are covalently bonded to one another, the second and third polypeptide

chains are covalently bonded to one another, and the third and fourth polypeptide chain, and wherein: (a) the first polypeptide chain comprises in the N-terminal to C-terminal direction: (i) a light chain variable domain of a first immunoglobulin (VL-1) that is capable of specifically binding to a first epitope; (ii) a light chain constant domain of the first immunoglobulin (CL-1); (iii) a flexible peptide linker comprising the amino acid sequence $(GGGGS)_3$ (SEQ ID NO: 2506); and (iv) a light chain variable domain of a second immunoglobulin (VL-2) that is linked to a complementary heavy chain variable domain of the second immunoglobulin (VH-2), or a heavy chain variable domain of a second immunoglobulin (VH-2) that is linked to a complementary light chain variable domain of the second immunoglobulin (VL-2), wherein the VL-2 and VH-2 are capable of specifically binding to a second epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ (SEQ ID NO: 2507) to form a single-chain variable fragment; (b) the second polypeptide comprises in the N-terminal to C-terminal direction: (i) a heavy chain variable domain of the first immunoglobulin (VH-1) that is capable of specifically binding to the first epitope; (ii) a first CH1 domain of the first immunoglobulin (CH1-1); and (iii) a first heterodimerization domain of the first immunoglobulin, wherein the first heterodimerization domain is incapable of forming a stable homodimer with another first heterodimerization domain; (c) the third polypeptide comprises in the N-terminal to C-terminal direction: (i) a heavy chain variable domain of a third immunoglobulin (VH-3) that is capable of specifically binding to the first epitope; (ii) a second CH1 domain of the third immunoglobulin (CH1-3); and (iii) a second heterodimerization domain of the third immunoglobulin, wherein the second heterodimerization domain comprises an amino acid sequence or a nucleic acid sequence that is distinct from the first heterodimerization domain of the first immunoglobulin, wherein the second heterodimerization domain is incapable of forming a stable homodimer with another second heterodimerization domain, and wherein the second heterodimerization domain of the third immunoglobulin is configured to form a heterodimer with the first heterodimerization domain of the first immunoglobulin; (d) the fourth polypeptide comprises in the N-terminal to C-terminal direction: (i) a light chain variable domain of the third immunoglobulin (VL-3) that is capable of specifically binding to the first epitope; (ii) a light chain constant domain of the third immunoglobulin (CL-3); (iii) a flexible peptide linker comprising the amino acid sequence $(GGGGS)_3$ (SEQ ID NO: 2506); and (iv) a light chain variable domain of a fourth immunoglobulin (VL-4) that is linked to a complementary heavy chain variable domain of the fourth immunoglobulin (VH-4), or a heavy chain variable domain of a fourth immunoglobulin (VH-4) that is linked to a complementary light chain variable domain of the fourth immunoglobulin (VL-4), wherein the VL-4 and VH-4 are capable of specifically binding to a third epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ (SEQ ID NO: 2507) to form a single-chain variable fragment, and wherein each of VL-2 and VL-4 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_L amino acid sequence selected from any one of SEQ ID NOs: 17, 25, 33, 41, 121, 137, 169, 177, 185, 193, 201, 209, 217, 225, 233, 241, 249, 257, 265, 321, 329, 337, 393, 401, 409, 473, 481, 489, 497, 505, 513, 545, 553, 561, 569, 577, 585, 593, 601, 625, 633, 641, 649, 657, 665, 673, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 785, 793, 801, 809, 817, 849, 857, 865, 873, 881, 889, 897, 905, 913, 921, 929, 937, 945, 969, 977, 1009, 1057, 1537, 1569, 1601, 1641, 1665, 1825, 1865, 1897, 1905, 1913, 1921, 1929, 2265, 2281 2289, 2329, and 2345; and/or wherein each of VH-2 and VH-4 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_H amino acid sequence selected from any one of SEQ ID NOs: 21, 29, 37, 45, 125, 141, 173, 181, 189, 197, 205, 213, 221, 229, 237, 245, 253, 261, 269, 325, 333, 341, 397, 405, 413, 477, 485, 493, 501, 509, 517, 549, 557, 565, 573, 581, 589, 597, 605, 629, 637, 645, 653, 661, 669, 677, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 789, 797, 805, 813, 821, 853, 861, 869, 877, 885, 893, 901, 909, 917, 925, 933, 941, 949, 973, 981, 1013, 1061, 1541, 1573, 1605, 1645, 1669, 1829, 1869, 1901, 1909, 1917, 1925, 1933, 2269, 2285, 2293, 2333, and 2349.

[0129] In another aspect, the present disclosure provides a heterodimeric multispecific antibody comprising a first polypeptide chain, a second polypeptide chain, a third polypeptide chain and a fourth polypeptide chain, wherein the first and second polypeptide chains are covalently bonded to one another, the second and third polypeptide chains are covalently bonded to one another, and the third and fourth polypeptide chain, and wherein: (a) the first polypeptide chain comprises in the N-terminal to C-terminal direction: (i) a light chain variable domain of a first immunoglobulin (VL-1) that is capable of specifically binding to a first epitope; (ii) a light chain constant domain of the first immunoglobulin (CL-1); (iii) a flexible peptide linker comprising the amino acid sequence $(GGGGS)_3$ (SEQ ID NO: 2506); and (iv) a light chain variable domain of a second immunoglobulin (VL-2) that is linked to a complementary heavy chain variable domain of the second immunoglobulin (VH-2), or a heavy chain variable domain of a second immunoglobulin (VH-2) that is linked to a complementary light chain variable domain of the second immunoglobulin (VL-2), wherein VL-2 and VH-2 are capable of specifically binding to a second epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ (SEQ ID NO: 2507) to form a single-chain variable fragment; (b) the second polypeptide comprises in the N-terminal to C-terminal direction: (i) a heavy chain variable domain of the first immunoglobulin (VH-1) that is capable of specifically binding to the first epitope; (ii) a first CH1 domain of the first immunoglobulin (CH1-1); and (iii) a first heterodimerization domain of the first immunoglobulin, wherein the first heterodimerization domain is incapable of forming a stable homodimer with another first heterodimerization domain; (c) the third polypeptide comprises in the N-terminal to C-terminal direction: (i) a heavy chain variable domain of a third immunoglobulin (VH-3) that is capable of specifically binding to a third epitope; (ii) a second CH1 domain of the third immunoglobulin (CH1-3); and (iii) a second heterodimerization domain of the third immunoglobulin, wherein the second heterodimerization domain comprises an amino acid sequence or a nucleic acid sequence that is distinct from the first heterodimerization domain of the first immunoglobulin, wherein the second heterodimerization domain is incapable of forming a stable homodimer with another second heterodimerization domain, and wherein the second heterodimerization domain of the third immunoglobulin is configured to form a heterodimer

with the first heterodimerization domain of the first immunoglobulin; (d) the fourth polypeptide comprises in the N-terminal to C-terminal direction: (i) a light chain variable domain of the third immunoglobulin (VL-3) that is capable of specifically binding to the third epitope; (ii) a light chain constant domain of the third immunoglobulin (CL-3); (iii) a flexible peptide linker comprising the amino acid sequence $(GGGGS)_3$ (SEQ ID NO: 2506); and (iv) a light chain variable domain of a fourth immunoglobulin (VL-4) that is linked to a complementary heavy chain variable domain of the fourth immunoglobulin (VH-4), or a heavy chain variable domain of a fourth immunoglobulin (VH-4) that is linked to a complementary light chain variable domain of the fourth immunoglobulin (VL-4), wherein VL-4 and VH-4 are capable of specifically binding to the fourth epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ (SEQ ID NO: 2507) to form a single-chain variable fragment; and wherein each of VL-1 and VL-3 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_L amino acid sequence selected from any one of SEQ ID NOs: 1, 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 105, 113, 121, 129, 145, 153, 161, 169, 177, 193, 201, 233, 241, 257, 273, 281, 289, 297, 305, 313, 321, 329, 337, 345, 353, 361, 369, 377, 385, 393, 401, 409, 417, 425, 433, 441, 449, 457, 465, 481, 489, 497, 521, 529, 537, 545, 553, 561, 609, 617, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 777, 785, 793, 801, 809, 817, 825, 833, 841, 849, 857, 865, 873, 881, 889, 945, 953, 961, 977, 985, 993, 1001, 1009, 1017, 1025, 1033, 1041, 1049, 1065, 1073, 1081, 1089, 1097, 1105, 1113, 1121, 1129, 1137, 1145, 1153, 1161, 1169, 1177, 1185, 1193, 1201, 1209, 1217, 1225, 1233, 1241, 1249, 1257, 1265, 1273, 1281, 1289, 1297, 1305, 1313, 1321, 1329, 1337, 1345, 1353, 1361, 1369, 1377, 1385, 1393, 1401, 1409, 1417, 1425, 1433, 1441, 1449, 1457, 1465, 1473, 1481, 1489, 1497, 1505, 1513, 1521, 1529, 1545, 1553, 1561, 1569, 1577, 1585, 1593, 1601, 1609, 1617, 1625, 1633, 1649, 1657, 1673, 1681, 1689, 1697, 1705, 1713, 1721, 1729, 1737, 1745, 1753, 1761, 1769, 1777, 1785, 1793, 1801, 1809, 1817, 1833, 1841, 1849, 1857, 1865, 1873, 1881, 1889, 1913, 1937, 1945, 1953, 1961, 1969, 1977, 1985, 1993, 2001, 2009, 2017, 2025, 2033, 2041, 2049, 2057, 2065, 2073, 2081, 2089, 2097, 2105, 2113, 2121, 2129, 2137, 2145, 2153, 2161, 2169, 2177, 2185, 2193, 2201, 2209, 2217, 2225, 2233, 2241, 2249, 2257, 2265, 2273, 2281, 2297, 2305, 2313, 2321, 2329, 2337 and 2345; and/or wherein each of VH-1 and VH-3 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_H amino acid sequence selected from any one of SEQ ID NOs: 5, 13, 21, 29, 37, 45, 53, 61, 69, 77, 85, 93, 101, 109, 117, 125, 133, 149, 157, 165, 173, 181, 197, 205, 237, 245, 261, 277, 285, 293, 301, 309, 317, 325, 333, 341, 349, 357, 365, 373, 381, 389, 397, 405, 413, 421, 429, 437, 445, 453, 461, 469, 485, 493, 501, 525, 533, 541, 549, 557, 565, 613, 621, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 781, 789, 797, 805, 813, 821, 829, 837, 845, 853, 861, 869, 877, 885, 893, 949, 957, 965, 981, 989, 997, 1005, 1013, 1021, 1029, 1037, 1045, 1053, 1069, 1077, 1085, 1093, 1101, 1109, 1117, 1125, 1133, 1141, 1149, 1157, 1165, 1173, 1181, 1189, 1197, 1205, 1213, 1221, 1229, 1237, 1245, 1253, 1261, 1269, 1277, 1285, 1293, 1301, 1309, 1317, 1325, 1333, 1341, 1349, 1357, 1365, 1373, 1381, 1389, 1397, 1405, 1413, 1421, 1429, 1437, 1445, 1453, 1461, 1469, 1477, 1485, 1493, 1501, 1509, 1517, 1525, 1533, 1549, 1557, 1565, 1573, 1581, 1589, 1597, 1605, 1613, 1621, 1629, 1637, 1653, 1661, 1677, 1685, 1693, 1701, 1709, 1717, 1725, 1733, 1741, 1749, 1757, 1765, 1773, 1781, 1789, 1797, 1805, 1813, 1821, 1837, 1845, 1853, 1861, 1869, 1877, 1885, 1893, 1917, 1941, 1949, 1957, 1965, 1973, 1981, 1989, 1997, 2005, 2013, 2021, 2029, 2037, 2045, 2053, 2061, 2069, 2077, 2085, 2093, 2101, 2109, 2117, 2125, 2133, 2141, 2149, 2157, 2165, 2173, 2181, 2189, 2197, 2205, 2213, 2221, 2229, 2237, 2245, 2253, 2261, 2269, 2277, 2285, 2301, 2309, 2317, 2325, 2333, 2341, and 2349; and/or wherein each of VL-2 and VL-4 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_L amino acid sequence selected from any one of SEQ ID NOs: 17, 25, 33, 41, 121, 137, 169, 177, 185, 193, 201, 209, 217, 225, 233, 241, 249, 257, 265, 321, 329, 337, 393, 401, 409, 473, 481, 489, 497, 505, 513, 545, 553, 561, 569, 577, 585, 593, 601, 625, 633, 641, 649, 657, 665, 673, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 785, 793, 801, 809, 817, 849, 857, 865, 873, 881, 889, 897, 905, 913, 921, 929, 937, 945, 969, 977, 1009, 1057, 1537, 1569, 1601, 1641, 1665, 1825, 1865, 1897, 1905, 1913, 1921, 1929, 2265, 2281 2289, 2329, and 2345; and/or wherein each of VH-2 and VH-4 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_H amino acid sequence selected from any one of SEQ ID NOs: 21, 29, 37, 45, 125, 141, 173, 181, 189, 197, 205, 213, 221, 229, 237, 245, 253, 261, 269, 325, 333, 341, 397, 405, 413, 477, 485, 493, 501, 509, 517, 549, 557, 565, 573, 581, 589, 597, 605, 629, 637, 645, 653, 661, 669, 677, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 789, 797, 805, 813, 821, 853, 861, 869, 877, 885, 893, 901, 909, 917, 925, 933, 941, 949, 973, 981, 1013, 1061, 1541, 1573, 1605, 1645, 1669, 1829, 1869, 1901, 1909, 1917, 1925, 1933, 2269, 2285, 2293, 2333, and 2349.

[0130] In another aspect, the present disclosure provides a heterodimeric multispecific antibody comprising a first polypeptide chain, a second polypeptide chain, a third polypeptide chain and a fourth polypeptide chain, wherein the first and second polypeptide chains are covalently bonded to one another, the second and third polypeptide chains are covalently bonded to one another, and the third and fourth polypeptide chain, and wherein: (a) the first polypeptide chain comprises in the N-terminal to C-terminal direction: (i) a light chain variable domain of a first immunoglobulin (VL-1) that is capable of specifically binding to a first epitope; (ii) a light chain constant domain of the first immunoglobulin (CL-1); (iii) a flexible peptide linker comprising the amino acid sequence $(GGGGS)_3$ (SEQ ID NO: 2506); and (iv) a light chain variable domain of a second immunoglobulin (VL-2) that is linked to a complementary heavy chain variable domain of the second immunoglobulin (VH-2), or a heavy chain variable domain of a second immunoglobulin (VH-2) that is linked to a complementary light chain variable domain of the second immunoglobulin (VL-2), wherein VL-2 and VH-2 are capable of specifically binding to a second epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ (SEQ ID NO: 2507) to form a single-chain variable fragment; (b) the second polypeptide comprises in the N-terminal to C-terminal direction: (i) a heavy chain variable domain of the first immunoglobulin (VH-1) that is capable of specifically binding to the first epitope; (ii) a first CH1 domain of the first immunoglobulin (CH1-1); and (iii)

a first heterodimerization domain of the first immunoglobulin, wherein the first heterodimerization domain is incapable of forming a stable homodimer with another first heterodimerization domain; (c) the third polypeptide comprises in the N-terminal to C-terminal direction: (i) a heavy chain variable domain of a third immunoglobulin (VH-3) that is capable of specifically binding to the first epitope; (ii) a second CH1 domain of the third immunoglobulin (CH1-3); and (iii) a second heterodimerization domain of the third immunoglobulin, wherein the second heterodimerization domain comprises an amino acid sequence or a nucleic acid sequence that is distinct from the first heterodimerization domain of the first immunoglobulin, wherein the second heterodimerization domain is incapable of forming a stable homodimer with another second heterodimerization domain, and wherein the second heterodimerization domain of the third immunoglobulin is configured to form a heterodimer with the first heterodimerization domain of the first immunoglobulin; (d) the fourth polypeptide comprises in the N-terminal to C-terminal direction: (i) a light chain variable domain of the third immunoglobulin (VL-3) that is capable of specifically binding to the first epitope; and (ii) a light chain constant domain of the third immunoglobulin (CL-3); and wherein VL-2 comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_L amino acid sequence selected from any one of SEQ ID NOs: 17, 25, 33, 41, 121, 137, 169, 177, 185, 193, 201, 209, 217, 225, 233, 241, 249, 257, 265, 321, 329, 337, 393, 401, 409, 473, 481, 489, 497, 505, 513, 545, 553, 561, 569, 577, 585, 593, 601, 625, 633, 641, 649, 657, 665, 673, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 785, 793, 801, 809, 817, 849, 857, 865, 873, 881, 889, 897, 905, 913, 921, 929, 937, 945, 969, 977, 1009, 1057, 1537, 1569, 1601, 1641, 1665, 1825, 1865, 1897, 1905, 1913, 1921, 1929, 2265, 2281 2289, 2329, and 2345; and/or wherein VH-2 comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_H amino acid sequence selected from any one of SEQ ID NOs: 21, 29, 37, 45, 125, 141, 173, 181, 189, 197, 205, 213, 221, 229, 237, 245, 253, 261, 269, 325, 333, 341, 397, 405, 413, 477, 485, 493, 501, 509, 517, 549, 557, 565, 573, 581, 589, 597, 605, 629, 637, 645, 653, 661, 669, 677, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 789, 797, 805, 813, 821, 853, 861, 869, 877, 885, 893, 901, 909, 917, 925, 933, 941, 949, 973, 981, 1013, 1061, 1541, 1573, 1605, 1645, 1669, 1829, 1869, 1901, 1909, 1917, 1925, 1933, 2269, 2285, 2293, 2333, and 2349. In some embodiments, both VH-1 and VH-3 comprise the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_H amino acid sequence selected from any one of SEQ ID NOs: 5, 13, 21, 29, 37, 45, 53, 61, 69, 77, 85, 93, 101, 109, 117, 125, 133, 149, 157, 165, 173, 181, 197, 205, 237, 245, 261, 277, 285, 293, 301, 309, 317, 325, 333, 341, 349, 357, 365, 373, 381, 389, 397, 405, 413, 421, 429, 437, 445, 453, 461, 469, 485, 493, 501, 525, 533, 541, 549, 557, 565, 613, 621, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 781, 789, 797, 805, 813, 821, 829, 837, 845, 853, 861, 869, 877, 885, 893, 949, 957, 965, 981, 989, 997, 1005, 1013, 1021, 1029, 1037, 1045, 1053, 1069, 1077, 1085, 1093, 1101, 1109, 1117, 1125, 1133, 1141, 1149, 1157, 1165, 1173, 1181, 1189, 1197, 1205, 1213, 1221, 1229, 1237, 1245, 1253, 1261, 1269, 1277, 1285, 1293, 1301, 1309, 1317, 1325, 1333, 1341, 1349, 1357, 1365, 1373, 1381, 1389, 1397, 1405, 1413, 1421, 1429, 1437, 1445, 1453, 1461, 1469, 1477, 1485, 1493, 1501, 1509, 1517, 1525, 1533, 1549, 1557, 1565, 1573, 1581, 1589, 1597, 1605, 1613, 1621, 1629, 1637, 1653, 1661, 1677, 1685, 1693, 1701, 1709, 1717, 1725, 1733, 1741, 1749, 1757, 1765, 1773, 1781, 1789, 1797, 1805, 1813, 1821, 1837, 1845, 1853, 1861, 1869, 1877, 1885, 1893, 1917, 1941, 1949, 1957, 1965, 1973, 1981, 1989, 1997, 2005, 2013, 2021, 2029, 2037, 2045, 2053, 2061, 2069, 2077, 2085, 2093, 2101, 2109, 2117, 2125, 2133, 2141, 2149, 2157, 2165, 2173, 2181, 2189, 2197, 2205, 2213, 2221, 2229, 2237, 2245, 2253, 2261, 2269, 2277, 2285, 2301, 2309, 2317, 2325, 2333, 2341, and 2349; and/or both VL-1 and VL-3 comprise the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_L amino acid sequence selected from any one of SEQ ID NOs: 1, 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 105, 113, 121, 129, 145, 153, 161, 169, 177, 193, 201, 233, 241, 257, 273, 281, 289, 297, 305, 313, 321, 329, 337, 345, 353, 361, 369, 377, 385, 393, 401, 409, 417, 425, 433, 441, 449, 457, 465, 481, 489, 497, 521, 529, 537, 545, 553, 561, 609, 617, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 777, 785, 793, 801, 809, 817, 825, 833, 841, 849, 857, 865, 873, 881, 889, 945, 953, 961, 977, 985, 993, 1001, 1009, 1017, 1025, 1033, 1041, 1049, 1065, 1073, 1081, 1089, 1097, 1105, 1113, 1121, 1129, 1137, 1145, 1153, 1161, 1169, 1177, 1185, 1193, 1201, 1209, 1217, 1225, 1233, 1241, 1249, 1257, 1265, 1273, 1281, 1289, 1297, 1305, 1313, 1321, 1329, 1337, 1345, 1353, 1361, 1369, 1377, 1385, 1393, 1401, 1409, 1417, 1425, 1433, 1441, 1449, 1457, 1465, 1473, 1481, 1489, 1497, 1505, 1513, 1521, 1529, 1545, 1553, 1561, 1569, 1577, 1585, 1593, 1601, 1609, 1617, 1625, 1633, 1649, 1657, 1673, 1681, 1689, 1697, 1705, 1713, 1721, 1729, 1737, 1745, 1753, 1761, 1769, 1777, 1785, 1793, 1801, 1809, 1817, 1833, 1841, 1849, 1857, 1865, 1873, 1881, 1889, 1913, 1937, 1945, 1953, 1961, 1969, 1977, 1985, 1993, 2001, 2009, 2017, 2025, 2033, 2041, 2049, 2057, 2065, 2073, 2081, 2089, 2097, 2105, 2113, 2121, 2129, 2137, 2145, 2153, 2161, 2169, 2177, 2185, 2193, 2201, 2209, 2217, 2225, 2233, 2241, 2249, 2257, 2265, 2273, 2281, 2297, 2305, 2313, 2321, 2329, 2337 and 2345.

[0131] In yet another aspect, the present disclosure provides a heterodimeric multispecific antibody comprising a first polypeptide chain, a second polypeptide chain, a third polypeptide chain and a fourth polypeptide chain, wherein the first and second polypeptide chains are covalently bonded to one another, the second and third polypeptide chains are covalently bonded to one another, and the third and fourth polypeptide chain, and wherein: (a) the first polypeptide chain comprises in the N-terminal to C-terminal direction: (i) a light chain variable domain of a first immunoglobulin (VL-1) that is capable of specifically binding to a first epitope; (ii) a light chain constant domain of the first immunoglobulin (CL-1); (iii) a flexible peptide linker comprising the amino acid sequence $(GGGGS)_3$ (SEQ ID NO: 2506); and (iv) a light chain variable domain of a second immunoglobulin (VL-2) that is linked to a complementary heavy chain variable domain of the second immunoglobulin (VH-2), or a heavy chain variable domain of a second immunoglobulin (VH-2) that is linked to a complementary light chain variable domain of the second immunoglobulin (VL-2), wherein VL-2 and VH-2 are capable of specifically binding to a second epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ (SEQ ID NO: 2507) to form a single-chain variable fragment; (b) the second polypeptide comprises in

the N-terminal to C-terminal direction: (i) a heavy chain variable domain of the first immunoglobulin (VH-1) that is capable of specifically binding to the first epitope; (ii) a first CH1 domain of the first immunoglobulin (CH1-1); and (iii) a first heterodimerization domain of the first immunoglobulin, wherein the first heterodimerization domain is incapable of forming a stable homodimer with another first heterodimerization domain; (c) the third polypeptide comprises in the N-terminal to C-terminal direction: (i) a heavy chain variable domain of a third immunoglobulin (VH-3) that is capable of specifically binding to a third epitope; (ii) a second CH1 domain of the third immunoglobulin (CH1-3); and (iii) a second heterodimerization domain of the third immunoglobulin, wherein the second heterodimerization domain comprises an amino acid sequence or a nucleic acid sequence that is distinct from the first heterodimerization domain of the first immunoglobulin, wherein the second heterodimerization domain is incapable of forming a stable homodimer with another second heterodimerization domain, and wherein the second heterodimerization domain of the third immunoglobulin is configured to form a heterodimer with the first heterodimerization domain of the first immunoglobulin; (d) the fourth polypeptide comprises in the N-terminal to C-terminal direction: (i) a light chain variable domain of the third immunoglobulin (VL-3) that is capable of specifically binding to the third epitope; and (ii) a light chain constant domain of the third immunoglobulin (CL-3); and wherein each of VL-1 and VL-3 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_L amino acid sequence selected from any one of SEQ ID NOs: 1, 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 105, 113, 121, 129, 145, 153, 161, 169, 177, 193, 201, 233, 241, 257, 273, 281, 289, 297, 305, 313, 321, 329, 337, 345, 353, 361, 369, 377, 385, 393, 401, 409, 417, 425, 433, 441, 449, 457, 465, 481, 489, 497, 521, 529, 537, 545, 553, 561, 609, 617, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 777, 785, 793, 801, 809, 817, 825, 833, 841, 849, 857, 865, 873, 881, 889, 945, 953, 961, 977, 985, 993, 1001, 1009, 1017, 1025, 1033, 1041, 1049, 1065, 1073, 1081, 1089, 1097, 1105, 1113, 1121, 1129, 1137, 1145, 1153, 1161, 1169, 1177, 1185, 1193, 1201, 1209, 1217, 1225, 1233, 1241, 1249, 1257, 1265, 1273, 1281, 1289, 1297, 1305, 1313, 1321, 1329, 1337, 1345, 1353, 1361, 1369, 1377, 1385, 1393, 1401, 1409, 1417, 1425, 1433, 1441, 1449, 1457, 1465, 1473, 1481, 1489, 1497, 1505, 1513, 1521, 1529, 1545, 1553, 1561, 1569, 1577, 1585, 1593, 1601, 1609, 1617, 1625, 1633, 1649, 1657, 1673, 1681, 1689, 1697, 1705, 1713, 1721, 1729, 1737, 1745, 1753, 1761, 1769, 1777, 1785, 1793, 1801, 1809, 1817, 1833, 1841, 1849, 1857, 1865, 1873, 1881, 1889, 1913, 1937, 1945, 1953, 1961, 1969, 1977, 1985, 1993, 2001, 2009, 2017, 2025, 2033, 2041, 2049, 2057, 2065, 2073, 2081, 2089, 2097, 2105, 2113, 2121, 2129, 2137, 2145, 2153, 2161, 2169, 2177, 2185, 2193, 2201, 2209, 2217, 2225, 2233, 2241, 2249, 2257, 2265, 2273, 2281, 2297, 2305, 2313, 2321, 2329, 2337 and 2345; and/or wherein each of VH-1 and VH-3 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_H amino acid sequence selected from any one of SEQ ID NOs: 5, 13, 21, 29, 37, 45, 53, 61, 69, 77, 85, 93, 101, 109, 117, 125, 133, 149, 157, 165, 173, 181, 197, 205, 237, 245, 261, 277, 285, 293, 301, 309, 317, 325, 333, 341, 349, 357, 365, 373, 381, 389, 397, 405, 413, 421, 429, 437, 445, 453, 461, 469, 485, 493, 501, 525, 533, 541, 549, 557, 565, 613, 621, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 781, 789, 797, 805, 813, 821, 829, 837, 845, 853, 861, 869, 877, 885, 893, 949, 957, 965, 981, 989, 997, 1005, 1013, 1021, 1029, 1037, 1045, 1053, 1069, 1077, 1085, 1093, 1101, 1109, 1117, 1125, 1133, 1141, 1149, 1157, 1165, 1173, 1181, 1189, 1197, 1205, 1213, 1221, 1229, 1237, 1245, 1253, 1261, 1269, 1277, 1285, 1293, 1301, 1309, 1317, 1325, 1333, 1341, 1349, 1357, 1365, 1373, 1381, 1389, 1397, 1405, 1413, 1421, 1429, 1437, 1445, 1453, 1461, 1469, 1477, 1485, 1493, 1501, 1509, 1517, 1525, 1533, 1549, 1557, 1565, 1573, 1581, 1589, 1597, 1605, 1613, 1621, 1629, 1637, 1653, 1661, 1677, 1685, 1693, 1701, 1709, 1717, 1725, 1733, 1741, 1749, 1757, 1765, 1773, 1781, 1789, 1797, 1805, 1813, 1821, 1837, 1845, 1853, 1861, 1869, 1877, 1885, 1893, 1917, 1941, 1949, 1957, 1965, 1973, 1981, 1989, 1997, 2005, 2013, 2021, 2029, 2037, 2045, 2053, 2061, 2069, 2077, 2085, 2093, 2101, 2109, 2117, 2125, 2133, 2141, 2149, 2157, 2165, 2173, 2181, 2189, 2197, 2205, 2213, 2221, 2229, 2237, 2245, 2253, 2261, 2269, 2277, 2285, 2301, 2309, 2317, 2325, 2333, 2341, and 2349; and/or wherein VL-2 comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_L amino acid sequence selected from any one of SEQ ID NOs: 17, 25, 33, 41, 121, 137, 169, 177, 185, 193, 201, 209, 217, 225, 233, 241, 249, 257, 265, 321, 329, 337, 393, 401, 409, 473, 481, 489, 497, 505, 513, 545, 553, 561, 569, 577, 585, 593, 601, 625, 633, 641, 649, 657, 665, 673, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 785, 793, 801, 809, 817, 849, 857, 865, 873, 881, 889, 897, 905, 913, 921, 929, 937, 945, 969, 977, 1009, 1057, 1537, 1569, 1601, 1641, 1665, 1825, 1865, 1897, 1905, 1913, 1921, 1929, 2265, 2281 2289, 2329, and 2345; and/or wherein VH-2 comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_H amino acid sequence selected from any one of SEQ ID NOs: 21, 29, 37, 45, 125, 141, 173, 181, 189, 197, 205, 213, 221, 229, 237, 245, 253, 261, 269, 325, 333, 341, 397, 405, 413, 477, 485, 493, 501, 509, 517, 549, 557, 565, 573, 581, 589, 597, 605, 629, 637, 645, 653, 661, 669, 677, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 789, 797, 805, 813, 821, 853, 861, 869, 877, 885, 893, 901, 909, 917, 925, 933, 941, 949, 973, 981, 1013, 1061, 1541, 1573, 1605, 1645, 1669, 1829, 1869, 1901, 1909, 1917, 1925, 1933, 2269, 2285, 2293, 2333, and 2349.

[0132] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, VH-1 or VH-3 comprises an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 99% or 100% identical to a V_H amino acid sequence selected from any one of SEQ ID NOs: 5, 13, 21, 29, 37, 45, 53, 61, 69, 77, 85, 93, 101, 109, 117, 125, 133, 149, 157, 165, 173, 181, 197, 205, 237, 245, 261, 277, 285, 293, 301, 309, 317, 325, 333, 341, 349, 357, 365, 373, 381, 389, 397, 405, 413, 421, 429, 437, 445, 453, 461, 469, 485, 493, 501, 525, 533, 541, 549, 557, 565, 613, 621, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 781, 789, 797, 805, 813, 821, 829, 837, 845, 853, 861, 869, 877, 885, 893, 949, 957, 965, 981, 989, 997, 1005, 1013, 1021, 1029, 1037, 1045, 1053, 1069, 1077, 1085, 1093, 1101, 1109, 1117, 1125, 1133, 1141, 1149, 1157, 1165, 1173, 1181, 1189, 1197, 1205, 1213, 1221, 1229, 1237, 1245, 1253, 1261, 1269, 1277, 1285, 1293, 1301, 1309, 1317, 1325, 1333, 1341, 1349, 1357, 1365, 1373, 1381, 1389, 1397, 1405, 1413, 1421, 1429, 1437, 1445, 1453, 1461, 1469, 1477,

1485, 1493, 1501, 1509, 1517, 1525, 1533, 1549, 1557, 1565, 1573, 1581, 1589, 1597, 1605, 1613, 1621, 1629, 1637, 1653, 1661, 1677, 1685, 1693, 1701, 1709, 1717, 1725, 1733, 1741, 1749, 1757, 1765, 1773, 1781, 1789, 1797, 1805, 1813, 1821, 1837, 1845, 1853, 1861, 1869, 1877, 1885, 1893, 1917, 1941, 1949, 1957, 1965, 1973, 1981, 1989, 1997, 2005, 2013, 2021, 2029, 2037, 2045, 2053, 2061, 2069, 2077, 2085, 2093, 2101, 2109, 2117, 2125, 2133, 2141, 2149, 2157, 2165, 2173, 2181, 2189, 2197, 2205, 2213, 2221, 2229, 2237, 2245, 2253, 2261, 2269, 2277, 2285, 2301, 2309, 2317, 2325, 2333, 2341, and 2349; and/or the VL-1 or VL-3 comprises an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 99% or 100% identical to a V_L amino acid sequence selected from any one of SEQ ID NOs: 1, 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 105, 113, 121, 129, 145, 153, 161, 169, 177, 193, 201, 233, 241, 257, 273, 281, 289, 297, 305, 313, 321, 329, 337, 345, 353, 361, 369, 377, 385, 393, 401, 409, 417, 425, 433, 441, 449, 457, 465, 481, 489, 497, 521, 529, 537, 545, 553, 561, 609, 617, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 777, 785, 793, 801, 809, 817, 825, 833, 841, 849, 857, 865, 873, 881, 889, 945, 953, 961, 977, 985, 993, 1001, 1009, 1017, 1025, 1033, 1041, 1049, 1065, 1073, 1081, 1089, 1097, 1105, 1113, 1121, 1129, 1137, 1145, 1153, 1161, 1169, 1177, 1185, 1193, 1201, 1209, 1217, 1225, 1233, 1241, 1249, 1257, 1265, 1273, 1281, 1289, 1297, 1305, 1313, 1321, 1329, 1337, 1345, 1353, 1361, 1369, 1377, 1385, 1393, 1401, 1409, 1417, 1425, 1433, 1441, 1449, 1457, 1465, 1473, 1481, 1489, 1497, 1505, 1513, 1521, 1529, 1545, 1553, 1561, 1569, 1577, 1585, 1593, 1601, 1609, 1617, 1625, 1633, 1649, 1657, 1673, 1681, 1689, 1697, 1705, 1713, 1721, 1729, 1737, 1745, 1753, 1761, 1769, 1777, 1785, 1793, 1801, 1809, 1817, 1833, 1841, 1849, 1857, 1865, 1873, 1881, 1889, 1913, 1937, 1945, 1953, 1961, 1969, 1977, 1985, 1993, 2001, 2009, 2017, 2025, 2033, 2041, 2049, 2057, 2065, 2073, 2081, 2089, 2097, 2105, 2113, 2121, 2129, 2137, 2145, 2153, 2161, 2169, 2177, 2185, 2193, 2201, 2209, 2217, 2225, 2233, 2241, 2249, 2257, 2265, 2273, 2281, 2297, 2305, 2313, 2321, 2329, 2337 and 2345.

[0133] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, VH-2 or VH-4 comprises an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 99% or 100% identical to a V_H amino acid sequence selected from any one of SEQ ID NOs: 21, 29, 37, 45, 125, 141, 173, 181, 189, 197, 205, 213, 221, 229, 237, 245, 253, 261, 269, 325, 333, 341, 397, 405, 413, 477, 485, 493, 501, 509, 517, 549, 557, 565, 573, 581, 589, 597, 605, 629, 637, 645, 653, 661, 669, 677, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 789, 797, 805, 813, 821, 853, 861, 869, 877, 885, 893, 901, 909, 917, 925, 933, 941, 949, 973, 981, 1013, 1061, 1541, 1573, 1605, 1645, 1669, 1829, 1869, 1901, 1909, 1917, 1925, 1933, 2269, 2285, 2293, 2333, and 2349; and/or VL-2 or VL-4 comprises an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or 100% identical to a V_L amino acid sequence selected from any one of SEQ ID NOs: 17, 25, 33, 41, 121, 137, 169, 177, 185, 193, 201, 209, 217, 225, 233, 241, 249, 257, 265, 321, 329, 337, 393, 401, 409, 473, 481, 489, 497, 505, 513, 545, 553, 561, 569, 577, 585, 593, 601, 625, 633, 641, 649, 657, 665, 673, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 785, 793, 801, 809, 817, 849, 857, 865, 873, 881, 889, 897, 905, 913, 921, 929, 937, 945, 969, 977, 1009, 1057, 1537, 1569, 1601, 1641, 1665, 1825, 1865, 1897, 1905, 1913, 1921, 1929, 2265, 2281 2289, 2329, and 2345.

[0134] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, each of VL-1 and VH-1 comprise a V_L amino acid sequence and a V_H amino acid sequence selected from the group consisting of SEQ ID NOs: 1 and 5 respectively; SEQ ID NOs: 9 and 13 respectively; SEQ ID NOs: 17 and 21 respectively; SEQ ID NOs: 25 and 29 respectively; SEQ ID NOs: 33 and 37 respectively; SEQ ID NOs: 41 and 45 respectively; SEQ ID NOs: 49 and 53 respectively; SEQ ID NOs: 57 and 61 respectively; SEQ ID NOs: 73 and 77 respectively; SEQ ID NOs: 89 and 93 respectively; SEQ ID NOs: 97 and 101 respectively; SEQ ID NOs: 105 and 109 respectively; SEQ ID NOs: 113 and 117 respectively; SEQ ID NOs: 121 and 125 respectively; SEQ ID NOs: 129 and 133 respectively; SEQ ID NOs: 145 and 149 respectively; SEQ ID NOs: 161 and 165 respectively; SEQ ID NOs: 169 and 173 respectively; SEQ ID NOs: 177 and 181 respectively; SEQ ID NOs: 193 and 197 respectively; SEQ ID NOs: 201 and 205 respectively; SEQ ID NOs: 233 and 237 respectively; SEQ ID NOs: 241 and 245 respectively; SEQ ID NOs: 257 and 261 respectively; SEQ ID NOs: 273 and 277 respectively; SEQ ID NOs: 281 and 285 respectively; SEQ ID NOs: 289 and 293 respectively; SEQ ID NOs: 297 and 301 respectively; SEQ ID NOs: 305 and 309 respectively; SEQ ID NOs: 313 and 317 respectively; SEQ ID NOs: 321 and 325 respectively; SEQ ID NOs: 329 and 333 respectively; SEQ ID NOs: 337 and 341 respectively; SEQ ID NOs: 345 and 349 respectively; SEQ ID NOs: 353 and 357 respectively; SEQ ID NOs: 361 and 365 respectively; SEQ ID NOs: 369 and 373 respectively; SEQ ID NOs: 377 and 381 respectively; SEQ ID NOs: 385 and 389 respectively; SEQ ID NOs: 393 and 397 respectively; SEQ ID NOs: 401 and 405 respectively; SEQ ID NOs: 409 and 413 respectively; SEQ ID NOs: 417 and 421 respectively; SEQ ID NOs: 425 and 429 respectively; SEQ ID NOs: 433 and 437 respectively; SEQ ID NOs: 441 and 445 respectively; SEQ ID NOs: 449 and 453 respectively; SEQ ID NOs: 457 and 461 respectively; SEQ ID NOs: 465 and 469 respectively; SEQ ID NOs: 481 and 485 respectively; SEQ ID NOs: 489 and 493 respectively; SEQ ID NOs: 497 and 501 respectively; SEQ ID NOs: 521 and 525 respectively; SEQ ID NOs: 529 and 533 respectively; SEQ ID NOs: 537 and 541 respectively; SEQ ID NOs: 545 and 549 respectively; SEQ ID NOs: 553 and 557 respectively; SEQ ID NOs: 561 and 565 respectively; SEQ ID NOs: 609 and 613 respectively; SEQ ID NOs: 617 and 621 respectively; SEQ ID NOs: 681 and 685 respectively; SEQ ID NOs: 689 and 693 respectively; SEQ ID NOs: 697 and 701 respectively; SEQ ID NOs: 705 and 709 respectively; SEQ ID NOs: 713 and 717 respectively; SEQ ID NOs: 721 and 725 respectively; SEQ ID NOs: 729 and 733 respectively; SEQ ID NOs: 737 and 741 respectively; SEQ ID NOs: 745 and 749 respectively; SEQ ID NOs: 753 and 757 respectively; SEQ ID NOs: 761 and 765 respectively; SEQ ID NOs: 769 and 773 respectively; SEQ ID NOs: 785 and 789 respectively; SEQ ID NOs: 793 and 797 respectively; SEQ ID NOs: 801 and 805 respectively; SEQ ID NOs: 809 and 813 respectively; SEQ ID NOs: 817 and 821 respectively; SEQ ID NOs: 825 and 829 respectively; SEQ ID NOs: 833 and 837 respectively; SEQ ID NOs: 841 and 845 respectively; SEQ ID

NOs: 849 and 853 respectively; SEQ ID NOs: 857 and 861 respectively; SEQ ID NOs: 865 and 869 respectively; SEQ ID NOs: 873 and 877 respectively; SEQ ID NOs: 881 and 885 respectively; SEQ ID NOs: 889 and 893 respectively; SEQ ID NOs: 945 and 949 respectively; SEQ ID NOs: 953 and 957 respectively; SEQ ID NOs: 961 and 965 respectively; SEQ ID NOs: 977 and 981 respectively; SEQ ID NOs: 985 and 989 respectively; SEQ ID NOs: 993 and 997 respectively; SEQ ID NOs: 1001 and 1005 respectively; SEQ ID NOs: 1009 and 1013 respectively; SEQ ID NOs: 1017 and 1021 respectively; SEQ ID NOs: 1025 and 1029 respectively; SEQ ID NOs: 1033 and 1037 respectively; SEQ ID NOs: 1041 and 1045 respectively; SEQ ID NOs: 1065 and 1069 respectively; SEQ ID NOs: 1073 and 1077 respectively; SEQ ID NOs: 1081 and 1085 respectively; SEQ ID NOs: 1089 and 1093 respectively; SEQ ID NOs: 1097 and 1101 respectively; SEQ ID NOs: 1113 and 1117 respectively; SEQ ID NOs: 1121 and 1125 respectively; SEQ ID NOs: 1129 and 1133 respectively; SEQ ID NOs: 1137 and 1141 respectively; SEQ ID NOs: 1145 and 1149 respectively; SEQ ID NOs: 1153 and 1157 respectively; SEQ ID NOs: 1161 and 1165 respectively; SEQ ID NOs: 1169 and 1173 respectively; SEQ ID NOs: 1185 and 1189 respectively; SEQ ID NOs: 1193 and 1197 respectively; SEQ ID NOs: 1201 and 1205 respectively; SEQ ID NOs: 1209 and 1213 respectively; SEQ ID NOs: 1217 and 1221 respectively; SEQ ID NOs: 1225 and 1229 respectively; SEQ ID NOs: 1233 and 1237 respectively; SEQ ID NOs: 1241 and 1245 respectively; SEQ ID NOs: 1249 and 1253 respectively; SEQ ID NOs: 1257 and 1261 respectively; SEQ ID NOs: 1265 and 1269 respectively; SEQ ID NOs: 1273 and 1277 respectively; SEQ ID NOs: 1281 and 1285 respectively; SEQ ID NOs: 1289 and 1293 respectively; SEQ ID NOs: 1297 and 1301 respectively; SEQ ID NOs: 1305 and 1309 respectively; SEQ ID NOs: 1313 and 1317 respectively; SEQ ID NOs: 1321 and 1325 respectively; SEQ ID NOs: 1329 and 1333 respectively; SEQ ID NOs: 1337 and 1341 respectively; SEQ ID NOs: 1345 and 1349 respectively; SEQ ID NOs: 1353 and 1357 respectively; SEQ ID NOs: 1361 and 1365 respectively; SEQ ID NOs: 1369 and 1373 respectively; SEQ ID NOs: 1377 and 1381 respectively; SEQ ID NOs: 1385 and 1389 respectively; SEQ ID NOs: 1393 and 1397 respectively; SEQ ID NOs: 1401 and 1405 respectively; SEQ ID NOs: 1409 and 1413 respectively; SEQ ID NOs: 1417 and 1421 respectively; SEQ ID NOs: 1433 and 1437 respectively; SEQ ID NOs: 1441 and 1445 respectively; SEQ ID NOs: 1457 and 1461 respectively; SEQ ID NOs: 1465 and 1469 respectively; SEQ ID NOs: 1473 and 1477 respectively; SEQ ID NOs: 1481 and 1485 respectively; SEQ ID NOs: 1489 and 1493 respectively; SEQ ID NOs: 1497 and 1501 respectively; SEQ ID NOs: 1505 and 1509 respectively; SEQ ID NOs: 1513 and 1517 respectively; SEQ ID NOs: 1521 and 1525 respectively; SEQ ID NOs: 1529 and 1533 respectively; SEQ ID NOs: 1545 and 1549 respectively; SEQ ID NOs: 1553 and 1557 respectively; SEQ ID NOs: 1561 and 1565 respectively; SEQ ID NOs: 1569 and 1573 respectively; SEQ ID NOs: 1577 and 1581 respectively; SEQ ID NOs: 1585 and 1589 respectively; SEQ ID NOs: 1593 and 1597 respectively; SEQ ID NOs: 1601 and 1605 respectively; SEQ ID NOs: 1609 and 1613 respectively; SEQ ID NOs: 1617 and 1621 respectively; SEQ ID NOs: 1625 and 1629 respectively; SEQ ID NOs: 1633 and 1637 respectively; SEQ ID NOs: 1649 and 1653 respectively; SEQ ID NOs: 1657 and 1661 respectively; SEQ ID NOs: 1673 and 1677 respectively; SEQ ID NOs: 1681 and 1685 respectively; SEQ ID NOs: 1689 and 1693 respectively; SEQ ID NOs: 1697 and 1701 respectively; SEQ ID NOs: 1705 and 1709 respectively; SEQ ID NOs: 1713 and 1717 respectively; SEQ ID NOs: 1721 and 1725 respectively; SEQ ID NOs: 1729 and 1733 respectively; SEQ ID NOs: 1737 and 1741 respectively; SEQ ID NOs: 1745 and 1749 respectively; SEQ ID NOs: 1753 and 1757 respectively; SEQ ID NOs: 1761 and 1765 respectively; SEQ ID NOs: 1769 and 1773 respectively; SEQ ID NOs: 1777 and 1781 respectively; SEQ ID NOs: 1785 and 1789 respectively; SEQ ID NOs: 1793 and 1797 respectively; SEQ ID NOs: 1801 and 1805 respectively; SEQ ID NOs: 1809 and 1813 respectively; SEQ ID NOs: 1817 and 1821 respectively; SEQ ID NOs: 1833 and 1837 respectively; SEQ ID NOs: 1841 and 1845 respectively; SEQ ID NOs: 1849 and 1853 respectively; SEQ ID NOs: 1857 and 1861 respectively; SEQ ID NOs: 1865 and 1869 respectively; SEQ ID NOs: 1873 and 1877 respectively; SEQ ID NOs: 1881 and 1885 respectively; SEQ ID NOs: 1889 and 1893 respectively; SEQ ID NOs: 1913 and 1917 respectively; SEQ ID NOs: 1937 and 1941 respectively; SEQ ID NOs: 1945 and 1949 respectively; SEQ ID NOs: 1953 and 1957 respectively; SEQ ID NOs: 1961 and 1965 respectively; SEQ ID NOs: 1969 and 1973 respectively; SEQ ID NOs: 1977 and 1981 respectively; SEQ ID NOs: 1985 and 1989 respectively; SEQ ID NOs: 1993 and 1997 respectively; SEQ ID NOs: 2001 and 2005 respectively; SEQ ID NOs: 2009 and 2013 respectively; SEQ ID NOs: 2017 and 2021 respectively; SEQ ID NOs: 2025 and 2029 respectively; SEQ ID NOs: 2033 and 2037 respectively; SEQ ID NOs: 2041 and 2045 respectively; SEQ ID NOs: 2049 and 2053 respectively; SEQ ID NOs: 2057 and 2061 respectively; SEQ ID NOs: 2065 and 2069 respectively; SEQ ID NOs: 2073 and 2077 respectively; SEQ ID NOs: 2081 and 2085 respectively; SEQ ID NOs: 2089 and 2093 respectively; SEQ ID NOs: 2097 and 2101 respectively; SEQ ID NOs: 2105 and 2109 respectively; SEQ ID NOs: 2113 and 2117 respectively; SEQ ID NOs: 2121 and 2125 respectively; SEQ ID NOs: 2129 and 2133 respectively; SEQ ID NOs: 2137 and 2141 respectively; SEQ ID NOs: 2145 and 2149 respectively; SEQ ID NOs: 2153 and 2157 respectively; SEQ ID NOs: 2161 and 2165 respectively; SEQ ID NOs: 2169 and 2173 respectively; SEQ ID NOs: 2177 and 2181 respectively; SEQ ID NOs: 2185 and 2189 respectively; SEQ ID NOs: 2193 and 2197 respectively; SEQ ID NOs: 2201 and 2205 respectively; SEQ ID NOs: 2209 and 2213 respectively; SEQ ID NOs: 2217 and 2221 respectively; SEQ ID NOs: 2225 and 2229 respectively; SEQ ID NOs: 2233 and 2237 respectively; SEQ ID NOs: 2241 and 2245 respectively; SEQ ID NOs: 2249 and 2253 respectively; SEQ ID NOs: 2257 and 2261 respectively; SEQ ID NOs: 2273 and 2277 respectively; SEQ ID NOs: 2281 and 2285 respectively; SEQ ID NOs: 2305 and 2309 respectively; SEQ ID NOs: 2313 and 2317 respectively; SEQ ID NOs: 2321 and 2325 respectively; SEQ ID NOs: 2329 and 2333 respectively; SEQ ID NOs: 2337 and 2341 respectively; and SEQ ID NOs: 2345 and 2349 respectively.

[0135] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, each of VL-3 and VH-3 comprise a V_L amino acid sequence and a V_H amino acid sequence selected from the group consisting of SEQ ID NOs: 1 and 5 respectively;

SEQ ID NOs: 9 and 13 respectively; SEQ ID NOs: 17 and 21 respectively; SEQ ID NOs: 25 and 29 respectively; SEQ ID NOs: 33 and 37 respectively; SEQ ID NOs: 41 and 45 respectively; SEQ ID NOs: 49 and 53 respectively; SEQ ID NOs: 57 and 61 respectively; SEQ ID NOs: 73 and 77 respectively; SEQ ID NOs: 89 and 93 respectively; SEQ ID NOs: 97 and 101 respectively; SEQ ID NOs: 105 and 109 respectively; SEQ ID NOs: 113 and 117 respectively; SEQ ID NOs: 121 and 125 respectively; SEQ ID NOs: 129 and 133 respectively; SEQ ID NOs: 145 and 149 respectively; SEQ ID NOs: 161 and 165 respectively; SEQ ID NOs: 169 and 173 respectively; SEQ ID NOs: 177 and 181 respectively; SEQ ID NOs: 193 and 197 respectively; SEQ ID NOs: 201 and 205 respectively; SEQ ID NOs: 233 and 237 respectively; SEQ ID NOs: 241 and 245 respectively; SEQ ID NOs: 257 and 261 respectively; SEQ ID NOs: 273 and 277 respectively; SEQ ID NOs: 281 and 285 respectively; SEQ ID NOs: 289 and 293 respectively; SEQ ID NOs: 297 and 301 respectively; SEQ ID NOs: 305 and 309 respectively; SEQ ID NOs: 313 and 317 respectively; SEQ ID NOs: 321 and 325 respectively; SEQ ID NOs: 329 and 333 respectively; SEQ ID NOs: 337 and 341 respectively; SEQ ID NOs: 345 and 349 respectively; SEQ ID NOs: 353 and 357 respectively; SEQ ID NOs: 361 and 365 respectively; SEQ ID NOs: 369 and 373 respectively; SEQ ID NOs: 377 and 381 respectively; SEQ ID NOs: 385 and 389 respectively; SEQ ID NOs: 393 and 397 respectively; SEQ ID NOs: 401 and 405 respectively; SEQ ID NOs: 409 and 413 respectively; SEQ ID NOs: 417 and 421 respectively; SEQ ID NOs: 425 and 429 respectively; SEQ ID NOs: 433 and 437 respectively; SEQ ID NOs: 441 and 445 respectively; SEQ ID NOs: 449 and 453 respectively; SEQ ID NOs: 457 and 461 respectively; SEQ ID NOs: 465 and 469 respectively; SEQ ID NOs: 481 and 485 respectively; SEQ ID NOs: 489 and 493 respectively; SEQ ID NOs: 497 and 501 respectively; SEQ ID NOs: 521 and 525 respectively; SEQ ID NOs: 529 and 533 respectively; SEQ ID NOs: 537 and 541 respectively; SEQ ID NOs: 545 and 549 respectively; SEQ ID NOs: 553 and 557 respectively; SEQ ID NOs: 561 and 565 respectively; SEQ ID NOs: 609 and 613 respectively; SEQ ID NOs: 617 and 621 respectively; SEQ ID NOs: 681 and 685 respectively; SEQ ID NOs: 689 and 693 respectively; SEQ ID NOs: 697 and 701 respectively; SEQ ID NOs: 705 and 709 respectively; SEQ ID NOs: 713 and 717 respectively; SEQ ID NOs: 721 and 725 respectively; SEQ ID NOs: 729 and 733 respectively; SEQ ID NOs: 737 and 741 respectively; SEQ ID NOs: 745 and 749 respectively; SEQ ID NOs: 753 and 757 respectively; SEQ ID NOs: 761 and 765 respectively; SEQ ID NOs: 769 and 773 respectively; SEQ ID NOs: 785 and 789 respectively; SEQ ID NOs: 793 and 797 respectively; SEQ ID NOs: 801 and 805 respectively; SEQ ID NOs: 809 and 813 respectively; SEQ ID NOs: 817 and 821 respectively; SEQ ID NOs: 825 and 829 respectively; SEQ ID NOs: 833 and 837 respectively; SEQ ID NOs: 841 and 845 respectively; SEQ ID NOs: 849 and 853 respectively; SEQ ID NOs: 857 and 861 respectively; SEQ ID NOs: 865 and 869 respectively; SEQ ID NOs: 873 and 877 respectively; SEQ ID NOs: 881 and 885 respectively; SEQ ID NOs: 889 and 893 respectively; SEQ ID NOs: 945 and 949 respectively; SEQ ID NOs: 953 and 957 respectively; SEQ ID NOs: 961 and 965 respectively; SEQ ID NOs: 977 and 981 respectively; SEQ ID NOs: 985 and 989 respectively; SEQ ID NOs: 993 and 997 respectively; SEQ ID NOs: 1001 and 1005 respectively; SEQ ID NOs: 1009 and 1013 respectively; SEQ ID NOs: 1017 and 1021 respectively; SEQ ID NOs: 1025 and 1029 respectively; SEQ ID NOs: 1033 and 1037 respectively; SEQ ID NOs: 1041 and 1045 respectively; SEQ ID NOs: 1065 and 1069 respectively; SEQ ID NOs: 1073 and 1077 respectively; SEQ ID NOs: 1081 and 1085 respectively; SEQ ID NOs: 1089 and 1093 respectively; SEQ ID NOs: 1097 and 1101 respectively; SEQ ID NOs: 1113 and 1117 respectively; SEQ ID NOs: 1121 and 1125 respectively; SEQ ID NOs: 1129 and 1133 respectively; SEQ ID NOs: 1137 and 1141 respectively; SEQ ID NOs: 1145 and 1149 respectively; SEQ ID NOs: 1153 and 1157 respectively; SEQ ID NOs: 1161 and 1165 respectively; SEQ ID NOs: 1169 and 1173 respectively; SEQ ID NOs: 1185 and 1189 respectively; SEQ ID NOs: 1193 and 1197 respectively; SEQ ID NOs: 1201 and 1205 respectively; SEQ ID NOs: 1209 and 1213 respectively; SEQ ID NOs: 1217 and 1221 respectively; SEQ ID NOs: 1225 and 1229 respectively; SEQ ID NOs: 1233 and 1237 respectively; SEQ ID NOs: 1241 and 1245 respectively; SEQ ID NOs: 1249 and 1253 respectively; SEQ ID NOs: 1257 and 1261 respectively; SEQ ID NOs: 1265 and 1269 respectively; SEQ ID NOs: 1273 and 1277 respectively; SEQ ID NOs: 1281 and 1285 respectively; SEQ ID NOs: 1289 and 1293 respectively; SEQ ID NOs: 1297 and 1301 respectively; SEQ ID NOs: 1305 and 1309 respectively; SEQ ID NOs: 1313 and 1317 respectively; SEQ ID NOs: 1321 and 1325 respectively; SEQ ID NOs: 1329 and 1333 respectively; SEQ ID NOs: 1337 and 1341 respectively; SEQ ID NOs: 1345 and 1349 respectively; SEQ ID NOs: 1353 and 1357 respectively; SEQ ID NOs: 1361 and 1365 respectively; SEQ ID NOs: 1369 and 1373 respectively; SEQ ID NOs: 1377 and 1381 respectively; SEQ ID NOs: 1385 and 1389 respectively; SEQ ID NOs: 1393 and 1397 respectively; SEQ ID NOs: 1401 and 1405 respectively; SEQ ID NOs: 1409 and 1413 respectively; SEQ ID NOs: 1417 and 1421 respectively; SEQ ID NOs: 1433 and 1437 respectively; SEQ ID NOs: 1441 and 1445 respectively; SEQ ID NOs: 1457 and 1461 respectively; SEQ ID NOs: 1465 and 1469 respectively; SEQ ID NOs: 1473 and 1477 respectively; SEQ ID NOs: 1481 and 1485 respectively; SEQ ID NOs: 1489 and 1493 respectively; SEQ ID NOs: 1497 and 1501 respectively; SEQ ID NOs: 1505 and 1509 respectively; SEQ ID NOs: 1513 and 1517 respectively; SEQ ID NOs: 1521 and 1525 respectively; SEQ ID NOs: 1529 and 1533 respectively; SEQ ID NOs: 1545 and 1549 respectively; SEQ ID NOs: 1553 and 1557 respectively; SEQ ID NOs: 1561 and 1565 respectively; SEQ ID NOs: 1569 and 1573 respectively; SEQ ID NOs: 1577 and 1581 respectively; SEQ ID NOs: 1585 and 1589 respectively; SEQ ID NOs: 1593 and 1597 respectively; SEQ ID NOs: 1601 and 1605 respectively; SEQ ID NOs: 1609 and 1613 respectively; SEQ ID NOs: 1617 and 1621 respectively; SEQ ID NOs: 1625 and 1629 respectively; SEQ ID NOs: 1633 and 1637 respectively; SEQ ID NOs: 1649 and 1653 respectively; SEQ ID NOs: 1657 and 1661 respectively; SEQ ID NOs: 1673 and 1677 respectively; SEQ ID NOs: 1681 and 1685 respectively; SEQ ID NOs: 1689 and 1693 respectively; SEQ ID NOs: 1697 and 1701 respectively; SEQ ID NOs: 1705 and 1709 respectively; SEQ ID NOs: 1713 and 1717 respectively; SEQ ID NOs: 1721 and 1725 respectively; SEQ ID NOs: 1729 and 1733 respectively; SEQ ID NOs: 1737 and 1741 respectively; SEQ ID NOs: 1745 and 1749 respectively; SEQ ID NOs: 1753 and 1757 respectively; SEQ ID NOs:

1761 and 1765 respectively; SEQ ID NOs: 1769 and 1773 respectively; SEQ ID NOs: 1777 and 1781 respectively; SEQ ID NOs: 1785 and 1789 respectively; SEQ ID NOs: 1793 and 1797 respectively; SEQ ID NOs: 1801 and 1805 respectively; SEQ ID NOs: 1809 and 1813 respectively; SEQ ID NOs: 1817 and 1821 respectively; SEQ ID NOs: 1833 and 1837 respectively; SEQ ID NOs: 1841 and 1845 respectively; SEQ ID NOs: 1849 and 1853 respectively; SEQ ID NOs: 1857 and 1861 respectively; SEQ ID NOs: 1865 and 1869 respectively; SEQ ID NOs: 1873 and 1877 respectively; SEQ ID NOs: 1881 and 1885 respectively; SEQ ID NOs: 1889 and 1893 respectively; SEQ ID NOs: 1913 and 1917 respectively; SEQ ID NOs: 1937 and 1941 respectively; SEQ ID NOs: 1945 and 1949 respectively; SEQ ID NOs: 1953 and 1957 respectively; SEQ ID NOs: 1961 and 1965 respectively; SEQ ID NOs: 1969 and 1973 respectively; SEQ ID NOs: 1977 and 1981 respectively; SEQ ID NOs: 1985 and 1989 respectively; SEQ ID NOs: 1993 and 1997 respectively; SEQ ID NOs: 2001 and 2005 respectively; SEQ ID NOs: 2009 and 2013 respectively; SEQ ID NOs: 2017 and 2021 respectively; SEQ ID NOs: 2025 and 2029 respectively; SEQ ID NOs: 2033 and 2037 respectively; SEQ ID NOs: 2041 and 2045 respectively; SEQ ID NOs: 2049 and 2053 respectively; SEQ ID NOs: 2057 and 2061 respectively; SEQ ID NOs: 2065 and 2069 respectively; SEQ ID NOs: 2073 and 2077 respectively; SEQ ID NOs: 2081 and 2085 respectively; SEQ ID NOs: 2089 and 2093 respectively; SEQ ID NOs: 2097 and 2101 respectively; SEQ ID NOs: 2105 and 2109 respectively; SEQ ID NOs: 2113 and 2117 respectively; SEQ ID NOs: 2121 and 2125 respectively; SEQ ID NOs: 2129 and 2133 respectively; SEQ ID NOs: 2137 and 2141 respectively; SEQ ID NOs: 2145 and 2149 respectively; SEQ ID NOs: 2153 and 2157 respectively; SEQ ID NOs: 2161 and 2165 respectively; SEQ ID NOs: 2169 and 2173 respectively; SEQ ID NOs: 2177 and 2181 respectively; SEQ ID NOs: 2185 and 2189 respectively; SEQ ID NOs: 2193 and 2197 respectively; SEQ ID NOs: 2201 and 2205 respectively; SEQ ID NOs: 2209 and 2213 respectively; SEQ ID NOs: 2217 and 2221 respectively; SEQ ID NOs: 2225 and 2229 respectively; SEQ ID NOs: 2233 and 2237 respectively; SEQ ID NOs: 2241 and 2245 respectively; SEQ ID NOs: 2249 and 2253 respectively; SEQ ID NOs: 2257 and 2261 respectively; SEQ ID NOs: 2273 and 2277 respectively; SEQ ID NOs: 2281 and 2285 respectively; SEQ ID NOs: 2305 and 2309 respectively; SEQ ID NOs: 2313 and 2317 respectively; SEQ ID NOs: 2321 and 2325 respectively; SEQ ID NOs: 2329 and 2333 respectively; SEQ ID NOs: 2337 and 2341 respectively; and SEQ ID NOs: 2345 and 2349 respectively.

[0136] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, each of VL-1 and VH-1 comprise a V_L amino acid sequence and a V_H amino acid sequence selected from the group consisting of SEQ ID NOs: 9 and 13 respectively; SEQ ID NOs: 49 and 53 respectively; SEQ ID NOs: 57 and 61 respectively; SEQ ID NOs: 65 and 69 respectively; SEQ ID NOs: 81 and 85 respectively; SEQ ID NOs: 153 and 157 respectively; SEQ ID NOs: 161 and 165 respectively; SEQ ID NOs: 193 and 197 respectively; SEQ ID NOs: 201 and 205 respectively; SEQ ID NOs: 273 and 277 respectively; SEQ ID NOs: 281 and 285 respectively; SEQ ID NOs: 289 and 293 respectively; SEQ ID NOs: 297 and 301 respectively; SEQ ID NOs: 305 and 309 respectively; SEQ ID NOs: 313 and 317 respectively; SEQ ID NOs: 361 and 365 respectively; SEQ ID NOs: 377 and 381 respectively; SEQ ID NOs: 393 and 397 respectively; SEQ ID NOs: 401 and 405 respectively; SEQ ID NOs: 409 and 413 respectively; SEQ ID NOs: 417 and 421 respectively; SEQ ID NOs: 425 and 429 respectively; SEQ ID NOs: 433 and 437 respectively; SEQ ID NOs: 441 and 445 respectively; SEQ ID NOs: 449 and 453 respectively; SEQ ID NOs: 457 and 461 respectively; SEQ ID NOs: 465 and 469 respectively; SEQ ID NOs: 681 and 685 respectively; SEQ ID NOs: 689 and 693 respectively; SEQ ID NOs: 697 and 701 respectively; SEQ ID NOs: 705 and 709 respectively; SEQ ID NOs: 713 and 717 respectively; SEQ ID NOs: 721 and 725 respectively; SEQ ID NOs: 737 and 741 respectively; SEQ ID NOs: 745 and 749 respectively; SEQ ID NOs: 753 and 757 respectively; SEQ ID NOs: 761 and 765 respectively; SEQ ID NOs: 777 and 781 respectively; SEQ ID NOs: 825 and 829 respectively; SEQ ID NOs: 833 and 837 respectively; SEQ ID NOs: 841 and 845 respectively; SEQ ID NOs: 953 and 957 respectively; SEQ ID NOs: 961 and 965 respectively; SEQ ID NOs: 977 and 981 respectively; SEQ ID NOs: 993 and 997 respectively; SEQ ID NOs: 1001 and 1005 respectively; SEQ ID NOs: 1009 and 1013 respectively; SEQ ID NOs: 1017 and 1021 respectively; SEQ ID NOs: 1033 and 1037 respectively; SEQ ID NOs: 1049 and 1053 respectively; SEQ ID NOs: 1073 and 1077 respectively; SEQ ID NOs: 1081 and 1085 respectively; SEQ ID NOs: 1089 and 1093 respectively; SEQ ID NOs: 1105 and 1109 respectively; SEQ ID NOs: 1129 and 1133 respectively; SEQ ID NOs: 1137 and 1141 respectively; SEQ ID NOs: 1153 and 1157 respectively; SEQ ID NOs: 1161 and 1165 respectively; SEQ ID NOs: 1177 and 1181 respectively; SEQ ID NOs: 1225 and 1229 respectively; SEQ ID NOs: 1241 and 1245 respectively; SEQ ID NOs: 1257 and 1261 respectively; SEQ ID NOs: 1265 and 1269 respectively; SEQ ID NOs: 1297 and 1301 respectively; SEQ ID NOs: 1393 and 1397 respectively; SEQ ID NOs: 1409 and 1413 respectively; SEQ ID NOs: 1425 and 1429 respectively; SEQ ID NOs: 1441 and 1445 respectively; SEQ ID NOs: 1449 and 1453 respectively; SEQ ID NOs: 1457 and 1461 respectively; SEQ ID NOs: 1465 and 1469 respectively; SEQ ID NOs: 1473 and 1477 respectively; SEQ ID NOs: 1481 and 1485 respectively; SEQ ID NOs: 1497 and 1501 respectively; SEQ ID NOs: 1505 and 1509 respectively; SEQ ID NOs: 1513 and 1517 respectively; SEQ ID NOs: 1521 and 1525 respectively; SEQ ID NOs: 1529 and 1533 respectively; SEQ ID NOs: 1545 and 1549 respectively; SEQ ID NOs: 1553 and 1557 respectively; SEQ ID NOs: 1561 and 1565 respectively; SEQ ID NOs: 1569 and 1573 respectively; SEQ ID NOs: 1577 and 1581 respectively; SEQ ID NOs: 1585 and 1589 respectively; SEQ ID NOs: 1609 and 1613 respectively; SEQ ID NOs: 1617 and 1621 respectively; SEQ ID NOs: 1649 and 1653 respectively; SEQ ID NOs: 1657 and 1661 respectively; SEQ ID NOs: 1673 and 1677 respectively; SEQ ID NOs: 1689 and 1693 respectively; SEQ ID NOs: 1697 and 1701 respectively; SEQ ID NOs: 1705 and 1709 respectively; SEQ ID NOs: 1713 and 1717 respectively; SEQ ID NOs: 1721 and 1725 respectively; SEQ ID NOs: 1729 and 1733 respectively; SEQ ID NOs: 1745 and 1749 respectively; SEQ ID NOs: 1753 and 1757 respectively; SEQ ID NOs: 1761 and 1765 respectively; SEQ ID NOs: 1769 and 1773 respectively; SEQ ID NOs: 1777 and 1781 respectively; SEQ ID NOs: 1785 and 1789 respectively; SEQ ID NOs: 1793 and

1797 respectively; SEQ ID NOs: 1817 and 1821 respectively; SEQ ID NOs: 1833 and 1837 respectively; SEQ ID NOs: 1841 and 1845 respectively; SEQ ID NOs: 1849 and 1853 respectively; SEQ ID NOs: 1857 and 1861 respectively; SEQ ID NOs: 1865 and 1869 respectively; SEQ ID NOs: 1889 and 1893 respectively; SEQ ID NOs: 2257 and 2261 respectively; SEQ ID NOs: 2265 and 2269 respectively; SEQ ID NOs: 2281 and 2285 respectively; SEQ ID NOs: 2297 and 2301 respectively; SEQ ID NOs: 2305 and 2309 respectively; SEQ ID NOs: 2313 and 2317 respectively; SEQ ID NOs: 2321 and 2325 respectively; SEQ ID NOs: 2329 and 2333 respectively; SEQ ID NOs: 2337 and 2341 respectively; and SEQ ID NOs: 2345 and 2349 respectively.

[0137] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, each of VL-3 and VH-3 comprise a V_L amino acid sequence and a V_H amino acid sequence selected from the group consisting of SEQ ID NOs: 9 and 13 respectively; SEQ ID NOs: 49 and 53 respectively; SEQ ID NOs: 57 and 61 respectively; SEQ ID NOs: 65 and 69 respectively; SEQ ID NOs: 81 and 85 respectively; SEQ ID NOs: 153 and 157 respectively; SEQ ID NOs: 161 and 165 respectively; SEQ ID NOs: 193 and 197 respectively; SEQ ID NOs: 201 and 205 respectively; SEQ ID NOs: 273 and 277 respectively; SEQ ID NOs: 281 and 285 respectively; SEQ ID NOs: 289 and 293 respectively; SEQ ID NOs: 297 and 301 respectively; SEQ ID NOs: 305 and 309 respectively; SEQ ID NOs: 313 and 317 respectively; SEQ ID NOs: 361 and 365 respectively; SEQ ID NOs: 377 and 381 respectively; SEQ ID NOs: 393 and 397 respectively; SEQ ID NOs: 401 and 405 respectively; SEQ ID NOs: 409 and 413 respectively; SEQ ID NOs: 417 and 421 respectively; SEQ ID NOs: 425 and 429 respectively; SEQ ID NOs: 433 and 437 respectively; SEQ ID NOs: 441 and 445 respectively; SEQ ID NOs: 449 and 453 respectively; SEQ ID NOs: 457 and 461 respectively; SEQ ID NOs: 465 and 469 respectively; SEQ ID NOs: 681 and 685 respectively; SEQ ID NOs: 689 and 693 respectively; SEQ ID NOs: 697 and 701 respectively; SEQ ID NOs: 705 and 709 respectively; SEQ ID NOs: 713 and 717 respectively; SEQ ID NOs: 721 and 725 respectively; SEQ ID NOs: 737 and 741 respectively; SEQ ID NOs: 745 and 749 respectively; SEQ ID NOs: 753 and 757 respectively; SEQ ID NOs: 761 and 765 respectively; SEQ ID NOs: 777 and 781 respectively; SEQ ID NOs: 825 and 829 respectively; SEQ ID NOs: 833 and 837 respectively; SEQ ID NOs: 841 and 845 respectively; SEQ ID NOs: 953 and 957 respectively; SEQ ID NOs: 961 and 965 respectively; SEQ ID NOs: 977 and 981 respectively; SEQ ID NOs: 993 and 997 respectively; SEQ ID NOs: 1001 and 1005 respectively; SEQ ID NOs: 1009 and 1013 respectively; SEQ ID NOs: 1017 and 1021 respectively; SEQ ID NOs: 1033 and 1037 respectively; SEQ ID NOs: 1049 and 1053 respectively; SEQ ID NOs: 1073 and 1077 respectively; SEQ ID NOs: 1081 and 1085 respectively; SEQ ID NOs: 1089 and 1093 respectively; SEQ ID NOs: 1105 and 1109 respectively; SEQ ID NOs: 1129 and 1133 respectively; SEQ ID NOs: 1137 and 1141 respectively; SEQ ID NOs: 1153 and 1157 respectively; SEQ ID NOs: 1161 and 1165 respectively; SEQ ID NOs: 1177 and 1181 respectively; SEQ ID NOs: 1225 and 1229 respectively; SEQ ID NOs: 1241 and 1245 respectively; SEQ ID NOs: 1257 and 1261 respectively; SEQ ID NOs: 1265 and 1269 respectively; SEQ ID NOs: 1297 and 1301 respectively; SEQ ID NOs: 1393 and 1397 respectively; SEQ ID NOs: 1409 and 1413 respectively; SEQ ID NOs: 1425 and 1429 respectively; SEQ ID NOs: 1441 and 1445 respectively; SEQ ID NOs: 1449 and 1453 respectively; SEQ ID NOs: 1457 and 1461 respectively; SEQ ID NOs: 1465 and 1469 respectively; SEQ ID NOs: 1473 and 1477 respectively; SEQ ID NOs: 1481 and 1485 respectively; SEQ ID NOs: 1497 and 1501 respectively; SEQ ID NOs: 1505 and 1509 respectively; SEQ ID NOs: 1513 and 1517 respectively; SEQ ID NOs: 1521 and 1525 respectively; SEQ ID NOs: 1529 and 1533 respectively; SEQ ID NOs: 1545 and 1549 respectively; SEQ ID NOs: 1553 and 1557 respectively; SEQ ID NOs: 1561 and 1565 respectively; SEQ ID NOs: 1569 and 1573 respectively; SEQ ID NOs: 1577 and 1581 respectively; SEQ ID NOs: 1585 and 1589 respectively; SEQ ID NOs: 1609 and 1613 respectively; SEQ ID NOs: 1617 and 1621 respectively; SEQ ID NOs: 1649 and 1653 respectively; SEQ ID NOs: 1657 and 1661 respectively; SEQ ID NOs: 1673 and 1677 respectively; SEQ ID NOs: 1689 and 1693 respectively; SEQ ID NOs: 1697 and 1701 respectively; SEQ ID NOs: 1705 and 1709 respectively; SEQ ID NOs: 1713 and 1717 respectively; SEQ ID NOs: 1721 and 1725 respectively; SEQ ID NOs: 1729 and 1733 respectively; SEQ ID NOs: 1745 and 1749 respectively; SEQ ID NOs: 1753 and 1757 respectively; SEQ ID NOs: 1761 and 1765 respectively; SEQ ID NOs: 1769 and 1773 respectively; SEQ ID NOs: 1777 and 1781 respectively; SEQ ID NOs: 1785 and 1789 respectively; SEQ ID NOs: 1793 and 1797 respectively; SEQ ID NOs: 1817 and 1821 respectively; SEQ ID NOs: 1833 and 1837 respectively; SEQ ID NOs: 1841 and 1845 respectively; SEQ ID NOs: 1849 and 1853 respectively; SEQ ID NOs: 1857 and 1861 respectively; SEQ ID NOs: 1865 and 1869 respectively; SEQ ID NOs: 1889 and 1893 respectively; SEQ ID NOs: 2257 and 2261 respectively; SEQ ID NOs: 2265 and 2269 respectively; SEQ ID NOs: 2281 and 2285 respectively; SEQ ID NOs: 2297 and 2301 respectively; SEQ ID NOs: 2305 and 2309 respectively; SEQ ID NOs: 2313 and 2317 respectively; SEQ ID NOs: 2321 and 2325 respectively; SEQ ID NOs: 2329 and 2333 respectively; SEQ ID NOs: 2337 and 2341 respectively; and SEQ ID NOs: 2345 and 2349 respectively.

[0138] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, each of VL-2 and VH-2 comprise a V_L amino acid sequence and a V_H amino acid sequence selected from the group consisting of SEQ ID NOs: 17 and 21 respectively; SEQ ID NOs: 25 and 29 respectively; SEQ ID NOs: 33 and 37 respectively; SEQ ID NOs: 41 and 45 respectively; SEQ ID NOs: 121 and 125 respectively; SEQ ID NOs: 137 and 141 respectively; SEQ ID NOs: 169 and 173 respectively; SEQ ID NOs: 177 and 181 respectively; SEQ ID NOs: 185 and 189 respectively; SEQ ID NOs: 193 and 197 respectively; SEQ ID NOs: 201 and 205 respectively; SEQ ID NOs: 209 and 213 respectively; SEQ ID NOs: 217 and 221 respectively; SEQ ID NOs: 225 and 229 respectively; SEQ ID NOs: 233 and 237 respectively; SEQ ID NOs: 241 and 245 respectively; SEQ ID NOs: 249 and 253 respectively; SEQ ID NOs: 257 and 261 respectively; SEQ ID NOs: 265 and 269 respectively; SEQ ID NOs: 321 and 325 respectively; SEQ ID NOs: 329 and 333 respectively; SEQ ID NOs: 337 and 341 respectively; SEQ ID NOs: 393 and 397 respectively; SEQ ID NOs: 401 and 405 respectively; SEQ ID NOs: 409 and 413 respectively; SEQ ID

NOs: 473 and 477 respectively; SEQ ID NOs: 481 and 485 respectively; SEQ ID NOs: 489 and 493 respectively; SEQ ID NOs: 497 and 501 respectively; SEQ ID NOs: 505 and 509 respectively; SEQ ID NOs: 513 and 517 respectively; SEQ ID NOs: 545 and 549 respectively; SEQ ID NOs: 553 and 557 respectively; SEQ ID NOs: 561 and 565 respectively; SEQ ID NOs: 569 and 573 respectively; SEQ ID NOs: 577 and 581 respectively; SEQ ID NOs: 585 and 589 respectively; SEQ ID NOs: 593 and 597 respectively; SEQ ID NOs: 601 and 605 respectively; SEQ ID NOs: 625 and 629 respectively; SEQ ID NOs: 633 and 637 respectively; SEQ ID NOs: 641 and 645 respectively; SEQ ID NOs: 649 and 653 respectively; SEQ ID NOs: 657 and 661 respectively; SEQ ID NOs: 665 and 669 respectively; SEQ ID NOs: 673 and 677 respectively; SEQ ID NOs: 681 and 685 respectively; SEQ ID NOs: 689 and 693 respectively; SEQ ID NOs: 697 and 701 respectively; SEQ ID NOs: 705 and 709 respectively; SEQ ID NOs: 713 and 717 respectively; SEQ ID NOs: 721 and 725 respectively; SEQ ID NOs: 729 and 733 respectively; SEQ ID NOs: 737 and 741 respectively; SEQ ID NOs: 745 and 749 respectively; SEQ ID NOs: 753 and 757 respectively; SEQ ID NOs: 761 and 765 respectively; SEQ ID NOs: 769 and 773 respectively; SEQ ID NOs: 785 and 789 respectively; SEQ ID NOs: 793 and 797 respectively; SEQ ID NOs: 801 and 805 respectively; SEQ ID NOs: 809 and 813 respectively; SEQ ID NOs: 817 and 821 respectively; SEQ ID NOs: 849 and 853 respectively; SEQ ID NOs: 857 and 861 respectively; SEQ ID NOs: 865 and 869 respectively; SEQ ID NOs: 873 and 877 respectively; SEQ ID NOs: 881 and 885 respectively; SEQ ID NOs: 889 and 893 respectively; SEQ ID NOs: 897 and 901 respectively; SEQ ID NOs: 905 and 909 respectively; SEQ ID NOs: 913 and 917 respectively; SEQ ID NOs: 921 and 925 respectively; SEQ ID NOs: 929 and 933 respectively; SEQ ID NOs: 937 and 941 respectively; SEQ ID NOs: 945 and 949 respectively; SEQ ID NOs: 969 and 973 respectively; SEQ ID NOs: 977 and 981 respectively; SEQ ID NOs: 1009 and 1013 respectively; SEQ ID NOs: 1057 and 1061 respectively; SEQ ID NOs: 1537 and 1541 respectively; SEQ ID NOs: 1569 and 1573 respectively; SEQ ID NOs: 1601 and 1605 respectively; SEQ ID NOs: 1641 and 1645 respectively; SEQ ID NOs: 1665 and 1669 respectively; SEQ ID NOs: 1825 and 1829 respectively; SEQ ID NOs: 1865 and 1869 respectively; SEQ ID NOs: 1897 and 1901 respectively; SEQ ID NOs: 1905 and 1909 respectively; SEQ ID NOs: 1913 and 1917 respectively; SEQ ID NOs: 1921 and 1925 respectively; SEQ ID NOs: 1929 and 1933 respectively; SEQ ID NOs: 2265 and 2269 respectively; SEQ ID NOs: 2281 and 2285 respectively; 2289 and 2293 respectively; 2329 and 2333 respectively; and SEQ ID NOs: 2345 and 2349, respectively.

[0139] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, each of VL-4 and VH-4 comprise a V_L amino acid sequence and a V_H amino acid sequence selected from the group consisting of SEQ ID NOs: 17 and 21 respectively; SEQ ID NOs: 25 and 29 respectively; SEQ ID NOs: 33 and 37 respectively; SEQ ID NOs: 41 and 45 respectively; SEQ ID NOs: 121 and 125 respectively; SEQ ID NOs: 137 and 141 respectively; SEQ ID NOs: 169 and 173 respectively; SEQ ID NOs: 177 and 181 respectively; SEQ ID NOs: 185 and 189 respectively; SEQ ID NOs: 193 and 197 respectively; SEQ ID NOs: 201 and 205 respectively; SEQ ID NOs: 209 and 213 respectively; SEQ ID NOs: 217 and 221 respectively; SEQ ID NOs: 225 and 229 respectively; SEQ ID NOs: 233 and 237 respectively; SEQ ID NOs: 241 and 245 respectively; SEQ ID NOs: 249 and 253 respectively; SEQ ID NOs: 257 and 261 respectively; SEQ ID NOs: 265 and 269 respectively; SEQ ID NOs: 321 and 325 respectively; SEQ ID NOs: 329 and 333 respectively; SEQ ID NOs: 337 and 341 respectively; SEQ ID NOs: 393 and 397 respectively; SEQ ID NOs: 401 and 405 respectively; SEQ ID NOs: 409 and 413 respectively; SEQ ID NOs: 473 and 477 respectively; SEQ ID NOs: 481 and 485 respectively; SEQ ID NOs: 489 and 493 respectively; SEQ ID NOs: 497 and 501 respectively; SEQ ID NOs: 505 and 509 respectively; SEQ ID NOs: 513 and 517 respectively; SEQ ID NOs: 545 and 549 respectively; SEQ ID NOs: 553 and 557 respectively; SEQ ID NOs: 561 and 565 respectively; SEQ ID NOs: 569 and 573 respectively; SEQ ID NOs: 577 and 581 respectively; SEQ ID NOs: 585 and 589 respectively; SEQ ID NOs: 593 and 597 respectively; SEQ ID NOs: 601 and 605 respectively; SEQ ID NOs: 625 and 629 respectively; SEQ ID NOs: 633 and 637 respectively; SEQ ID NOs: 641 and 645 respectively; SEQ ID NOs: 649 and 653 respectively; SEQ ID NOs: 657 and 661 respectively; SEQ ID NOs: 665 and 669 respectively; SEQ ID NOs: 673 and 677 respectively; SEQ ID NOs: 681 and 685 respectively; SEQ ID NOs: 689 and 693 respectively; SEQ ID NOs: 697 and 701 respectively; SEQ ID NOs: 705 and 709 respectively; SEQ ID NOs: 713 and 717 respectively; SEQ ID NOs: 721 and 725 respectively; SEQ ID NOs: 729 and 733 respectively; SEQ ID NOs: 737 and 741 respectively; SEQ ID NOs: 745 and 749 respectively; SEQ ID NOs: 753 and 757 respectively; SEQ ID NOs: 761 and 765 respectively; SEQ ID NOs: 769 and 773 respectively; SEQ ID NOs: 785 and 789 respectively; SEQ ID NOs: 793 and 797 respectively; SEQ ID NOs: 801 and 805 respectively; SEQ ID NOs: 809 and 813 respectively; SEQ ID NOs: 817 and 821 respectively; SEQ ID NOs: 849 and 853 respectively; SEQ ID NOs: 857 and 861 respectively; SEQ ID NOs: 865 and 869 respectively; SEQ ID NOs: 873 and 877 respectively; SEQ ID NOs: 881 and 885 respectively; SEQ ID NOs: 889 and 893 respectively; SEQ ID NOs: 897 and 901 respectively; SEQ ID NOs: 905 and 909 respectively; SEQ ID NOs: 913 and 917 respectively; SEQ ID NOs: 921 and 925 respectively; SEQ ID NOs: 929 and 933 respectively; SEQ ID NOs: 937 and 941 respectively; SEQ ID NOs: 945 and 949 respectively; SEQ ID NOs: 969 and 973 respectively; SEQ ID NOs: 977 and 981 respectively; SEQ ID NOs: 1009 and 1013 respectively; SEQ ID NOs: 1057 and 1061 respectively; SEQ ID NOs: 1537 and 1541 respectively; SEQ ID NOs: 1569 and 1573 respectively; SEQ ID NOs: 1601 and 1605 respectively; SEQ ID NOs: 1641 and 1645 respectively; SEQ ID NOs: 1665 and 1669 respectively; SEQ ID NOs: 1825 and 1829 respectively; SEQ ID NOs: 1865 and 1869 respectively; SEQ ID NOs: 1897 and 1901 respectively; SEQ ID NOs: 1905 and 1909 respectively; SEQ ID NOs: 1913 and 1917 respectively; SEQ ID NOs: 1921 and 1925 respectively; SEQ ID NOs: 1929 and 1933 respectively; SEQ ID NOs: 2265 and 2269 respectively; SEQ ID NOs: 2281 and 2285 respectively; 2289 and 2293 respectively; 2329 and 2333 respectively; and SEQ ID NOs: 2345 and 2349, respectively.

[0140] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, the first immunoglobulin or the third immunoglobulin binds to a cell surface antigen selected from the

group consisting of a2b b3 (Glycoprotein IIb/IIIa), a4, a4b7, a4b7+aEb7, a5, Activin receptor type-2B, ALK1, Alpha-synuclein, amyloid beta, APP, AXL, Blood Group A, CAIX, CCL-2, CD105 (endoglin), CD115 (CSF1R), CD116a (CSF2Ra), CD123, CD152 (CTLA4), CD184 (CXCR4), CD19, CD192 (CCR2), CD194 (CCR4), CD195 (CCR5), CD20, CD200, CD22, CD221 (IGF1R), CD248, CD25, CD257 (BAFF), CD26, CD262 (DR5), CD276 (B7H3), CD3, CD30 (TNFRSF8), CD319 (SLAMF7), CD33, CD332 (FGFR2), CD350 (FZD10), CD37, CD371 (CLEC12A), CD38, CD4, CD49b (a2), CD51 (a5), CD52, CD56, CD61 (a4b3), CD70, CD73 (NTSE), CD74, CEA, Claudin-18.2, cMET, CRLR, DLL3, DLL4, DNA/histone (H1) complex, EGFR, EpCAM, EGFR-HER3, EGFRvIII, EphA3, ERGT (GalNAc) Tn Antigen, FLT1, FOLR1, frizzled family receptor (FZD), Lewis Y, Lewis X, GCGR, GD2, GD2 α-acetyl, GD3, GM1, GM1 fucosyl, GM2, GPA33, GPNMB, GUCY2C, HER2, HER3, HGFR (cMET), IgHe, IGLF2, Kallikreins, LINGO1, LOXL2, Ly6/PLAUR domain-containing protein 3, MADCAM1, MAG, Mesothelin, MT1-MMP (MMP14), MUC1, Mucin SAC, NaPi2b, NeuGc-GM3, notch, NOTCH2/NOTCH3 receptors, oxLDL, P-selectin, PCSK9, PDGFRA, PDGFRa, phosphatidylserine, polysialic acid, PSMA, PVRL4, RGMA, CD240D Blood group D antigen, root plate-specific spondin 3, serum amyloid P component, STEAP-1, TACSTD2, TGFb, TWEAKR, TYRP1, VEGFR2, VSIR, CD171 (L1CAM), CD19, CD47, pMHC[NY-ESO1], pMHC[MART1], pMHC [MAGEA1], pMHC[Tyrosinase], pMHC[gp100], pMHC [MUC1], pMHC[tax], pMHC[WT-1], pMHC[EBNA-1], pMHC[LMP2], pMHC[hTERT], GPC3, CD80, CD23, and fibronectin extra domain-B. The first immunoglobulin and the third immunoglobulin may bind to the same epitope on a target cell or two different epitopes on a target cell. In some embodiments, the target cell is a cancer cell.

[0141] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, the second immunoglobulin or the fourth immunoglobulin bind to an epitope on a white blood cell, a monocyte, a lymphocyte, a granulocyte, a macrophage, a T cell, a NK cell, a B cell, a NKT cell, an ILC, or neutrophil.

[0142] In any of the above embodiments of the heterodimeric multispecific antibodies disclosed herein, the second immunoglobulin or the fourth immunoglobulin bind to an antigen selected from the group consisting of Dabigatran, a4, a4b7, a4b7+aEb7, a5, AXL, BnDOTA, CD11a (LFA-1), CD3, CD4, CD8, CD16, CD19, CD22, CD23, CD25, CD28, CD30 (TNFRSF8), CD33, CD38, CD40, CD40L, CD47, CD49b (a2), CD54 (ICAM-1), CD56, CD74, CD80, CD115 (CSF1R), CD116a (CSF2Ra), CD123, CD134 (OX40), CD137 (41BB), CD152 (CTLA4), CD184 (CXCR4), CD192 (CCR2), CD194 (CCR4), CD195 (CCR5), CD223 (LAG-3), CD252 (OX40L), CD254 (RANKL), CD262 (DR5), CD27, CD200, CD221 (IGF1R), CD248, CD274 (PD-L1), CD275 (ICOS-L), CD278 (ICOS), CD279 (PD-1), CD319 (SLAMF7), CD371 (CLEC12A), MADCAM1, MT1-MMP (MMP14), NKG2A, NRP1,TIGIT, VSIR, KIRDL1/2/3, and KIR2DL2. The second immunoglobulin and the fourth immunoglobulin may bind to the same epitope or different epitopes on a white blood cell, a monocyte, a lymphocyte, a granulocyte, a macrophage, a T cell, a NK cell, a B cell, a NKT cell, an ILC, or neutrophil. In some embodiments, the second immunoglobulin binds CD3 and the fourth immunoglobulin binds an immune cell receptor selected from the group consisting of CD4, CD8, CD25, CD28, CTLA4, OX40, ICOS, PD-1, PD-L1, 41BB, CD2, CD69, and CD45. In other embodiments, the second immunoglobulin binds CD16 and the fourth immunoglobulin binds an immune cell receptor selected from the group consisting of CD56, NKG2D, and KIRDL1/2/3. In certain embodiments, the fourth immunoglobulin binds to an agent selected from the group consisting of a cytokine, a nucleic acid, a hapten, a small molecule, a radionuclide, an immunotoxin, a vitamin, a peptide, a lipid, a carbohydrate, biotin, digoxin, or any conjugated variants thereof.

[0143] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, the first immunoglobulin and the third immunoglobulin bind to their respective epitopes with a monovalent affinity or an effective affinity between about 100 nM to about 100 pM. In certain embodiments, the first immunoglobulin and the third immunoglobulin bind to cell surface epitopes that are between 60 and 120 angstroms apart.

[0144] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, the first immunoglobulin and the third immunoglobulin bind to their respective epitopes with a monovalent affinity or an effective affinity that is less than 100 pM. In certain embodiments, the first immunoglobulin and the third immunoglobulin bind to cell surface epitopes that are up to 180 angstroms apart.

[0145] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, the first heterodimerization domain of the first immunoglobulin and/or the second heterodimerization domain of the third immunoglobulin is a CH2-CH3 domain and has an isotype selected from the group consisting of IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgM, IgD, and IgE. Non-limiting examples of constant region sequences include:

Human IgD constant region, Uniprot: P01880
(SEQ ID NO: 2381)
APTKAPDVFPIISGCRHPKDNSPVVLACLITGYHPTSVTVTWYMGTQSQP

QRTFPEIQRRDSYYMTSSQLSTPLQQWRQGEYKCVVQHTASKSKKEIFRW

PESPKAQASSVPTAQPQAEGSLAKATTAPATTRNTGRGGEEKKKEKEKEE

QEERETKTPECPSHTQPLGVYLLTPAVQDLWLRDKATFTCFVVGSDLKDA

HLTWEVAGKVPTGGVEEGLLERHSNGSQSQHSRLTLPRSLWNAGTSVTCT

LNHPSLPPQRLMALREPAAQAPVKLSLNLLASSDPPEAASWLLCEVSGFS

PPNILLMWLEDQREVNTSGFAPARPPPQPGSTTFWAWSVLRVPAPPSPQP

ATYTCVVSHEDSRTLLNASRSLEVSYVTDHGPMK

Human IgG1 constant region, Uniprot: P01857
(SEQ ID NO: 2382)
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV

HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEP

KSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS

HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK

EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC

-continued

LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW

QQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Human IgG2 constant region, Uniprot: P01859
(SEQ ID NO: 2383)

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV

HTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVER

KCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP

EVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKC

KVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKG

FYPSDISVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGN

VFSCSVMHEALHNHYTQKSLSLSPGK

Human IgG3 constant region, Uniprot: P01860
(SEQ ID NO: 2384)

ASTKGPSVFPLAPCSRSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV

HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNVNHKPSNTKVDKRVEL

KTPLGDTTHTCPRCPEPKSCDTPPPCPRCPEPKSCDTPPPCPRCPEPKSC

DTPPPCPRCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHED

PEVQFKWYVDGVEVHNAKTKPREEQYNSTFRVVSVLTVLHQDWLNGKEYK

CKVSNKALPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVK

GFYPSDIAVEWESSGQPENNYNTTPPMLDSDGSFFLYSKLTVDKSRWQQG

NIFSCSVMHEALHNRFTQKSLSLSPGK

Human IgM constant region, Uniprot: P01871
(SEQ ID NO: 2385)

GSASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITLSWKYKNNSDI

SSTRGFPSVLRGGKYAATSQVLLPSKDVMQGTDEHVVCKVQHPNGNKEKN

VPLPVIAELPPKVSVFVPPRDGFFGNPRKSKLICQATGFSPRQIQVSWLR

EGKQVGSGVTTDQVQAEAKESGPTTYKVTSTLTIKESDWLGQSMFTCRVD

HRGLTFQQNASSMCVPDQDTAIRVFAIPPSFASIFLTKSTKLTCLVTDLT

TYDSVTISWTRQNGEAVKTHTNISESHPNATFSAVGEASICEDDWNSGER

FTCTVTHTDLPSPLKQTISRPKGVALHRPDVYLLPPAREQLNLRESATIT

CLVTGFSPADVFVQWMQRGQPLSPEKYVTSAPMPEPQAPGRYFAHSILTV

SEEEWNTGETYTCVAHEALPNRVTERTVDKSTGKPTLYNVSLVMSDTAGT

CY

Human IgG4 constant region, Uniprot: P01861
(SEQ ID NO: 2386)

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV

HTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVES

KYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQED

PEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYK

CKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVK

GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEG

NVFSCSVMHEALHNHYTQKSLSLSLGK

-continued

Human IgA1 constant region, Uniprot: P01876
(SEQ ID NO: 2387)

ASPTSPKVFPLSLCSTQPDGNVVIACLVQGFFPQEPLSVTWSESGQGVTA

RNFPPSQDASGDLYTTSSQLTLPATQCLAGKSVTCHVKHYTNPSQDVTVP

CPVPSTPPTPSPSTPPTPSPSCCHPRLSLHRPALEDLLLGSEANLTCTLT

GLRDASGVTFTWTPSSGKSAVQGPPERDLCGCYSVSSVLPGCAEPWNHGK

TFTCTAAYPESKTPLTATLSKSGNTFRPEVHLLPPPSEELALNELVTLTC

LARGFSPKDVLVRWLQGSQELPREKYLTWASRQEPSQGTTTFAVTSILRV

AAEDWKKGDTFSCMVGHEALPLAFTQKTIDRLAGKPTHVNVSVVMAEVDG

TCY

Human IgA2 constant region, Uniprot: P01877
(SEQ ID NO: 2388)

ASPTSPKVFPLSLDSTPQDGNVVVACLVQGFFPQEPLSVTWSESGQNVTA

RNFPPSQDASGDLYTTSSQLTLPATQCPDGKSVTCHVKHYTNPSQDVTVP

CPVPPPPPCCHPRLSLHRPALEDLLLGSEANLTCTLTGLRDASGATFTWT

PSSGKSAVQGPPERDLCGCYSVSSVLPGCAQPWNHGETFTCTAAHPELKT

PLTANITKSGNTFRPEVHLLPPPSEELALNELVTLTCLARGFSPKDVLVR

WLQGSQELPREKYLTWASRQEPSQGTTTFAVTSILRVAAEDWKKGDTFSC

MVGHEALPLAFTQKTIDRMAGKPTHVNVSVVMAEVDGTCY

Human Ig kappa constant region, Uniprot: P01834
(SEQ ID NO: 2389)

TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN

SQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKS

FNRGEC

[0146] In some embodiments, the immunoglobulin-related compositions of the present technology comprise a heavy chain constant region that is at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or is 100% identical to SEQ ID NOS: 2381-2388. Additionally or alternatively, in some embodiments, the immunoglobulin-related compositions of the present technology comprise a light chain constant region that is at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or is 100% identical to SEQ ID NO: 2389.

[0147] Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, the first heterodimerization domain of the first immunoglobulin and/or the second heterodimerization domain of the third immunoglobulin is an IgG1 constant region comprising one or more amino acid substitutions selected from the group consisting of N297A and K322A. Additionally or alternatively, in some embodiments of the heterodimeric multispecific antibodies disclosed herein, the first heterodimerization domain of the first immunoglobulin is a CH2-CH3 domain comprising a K409R mutation and the second heterodimerization domain of the third immunoglobulin is a CH2-CH3 domain comprising a F405L mutation.

[0148] Also disclosed herein are recombinant nucleic acid sequences encoding any of the antibodies described herein. In another aspect, the present technology provides a host cell or vector expressing any nucleic acid sequence encoding any immunoglobulin-related composition described herein.

[0149] In some embodiments, the immunoglobulin-related compositions of the present technology are chimeric, humanized, or monoclonal. The immunoglobulin-related compositions of the present technology can further be recombinantly fused to a heterologous polypeptide at the N or C terminus or chemically conjugated (including covalently and non-covalently conjugations) to polypeptides or other compositions. For example, the immunoglobulin-related compositions of the present technology can be recombinantly fused or conjugated to molecules useful as labels in detection assays and effector molecules such as heterologous polypeptides, drugs, or toxins. See, e.g., WO 92/08495; WO 91/14438; WO 89/12624; U.S. Pat. No. 5,314,995; and EP 0 396 387.

[0150] In any of the above embodiments of the immunoglobulin-related compositions of the present technology, the HDTVS antibody may be optionally conjugated to an agent selected from the group consisting of isotopes, dyes, chromagens, contrast agents, drugs, toxins, cytokines, enzymes, enzyme inhibitors, hormones, hormone antagonists, growth factors, radionuclides, metals, liposomes, nanoparticles, RNA, DNA or any combination thereof. For a chemical bond or physical bond, a functional group on the immunoglobulin-related composition typically associates with a functional group on the agent. Alternatively, a functional group on the agent associates with a functional group on the immunoglobulin-related composition.

[0151] The functional groups on the agent and immunoglobulin-related composition can associate directly. For example, a functional group (e.g., a sulfhydryl group) on an agent can associate with a functional group (e.g., sulfhydryl group) on an immunoglobulin-related composition to form a disulfide. Alternatively, the functional groups can associate through a cross-linking agent (i.e., linker). Some examples of cross-linking agents are described below. The cross-linker can be attached to either the agent or the immunoglobulin-related composition. The number of agents or immunoglobulin-related compositions in a conjugate is also limited by the number of functional groups present on the other. For example, the maximum number of agents associated with a conjugate depends on the number of functional groups present on the immunoglobulin-related composition. Alternatively, the maximum number of immunoglobulin-related compositions associated with an agent depends on the number of functional groups present on the agent.

[0152] In yet another embodiment, the conjugate comprises one immunoglobulin-related composition associated to one agent. In one embodiment, a conjugate comprises at least one agent chemically bonded (e.g., conjugated) to at least one immunoglobulin-related composition. The agent can be chemically bonded to an immunoglobulin-related composition by any method known to those in the art. For example, a functional group on the agent may be directly attached to a functional group on the immunoglobulin-related composition. Some examples of suitable functional groups include, for example, amino, carboxyl, sulfhydryl, maleimide, isocyanate, isothiocyanate and hydroxyl.

[0153] The agent may also be chemically bonded to the immunoglobulin-related composition by means of cross-linking agents, such as dialdehydes, carbodiimides, dimaleimides, and the like. Cross-linking agents can, for example, be obtained from Pierce Biotechnology, Inc., Rockford, Ill. The Pierce Biotechnology, Inc. web-site can provide assistance. Additional cross-linking agents include the platinum cross-linking agents described in U.S. Pat. Nos. 5,580,990; 5,985,566; and 6,133,038 of Kreatech Biotechnology, B.V., Amsterdam, The Netherlands.

[0154] Alternatively, the functional group on the agent and immunoglobulin-related composition can be the same. Homobifunctional cross-linkers are typically used to cross-link identical functional groups. Examples of homobifunctional cross-linkers include EGS (i.e., ethylene glycol bis [succinimidylsuccinate]), DSS (i.e., disuccinimidyl suberate), DMA (i.e., dimethyl adipimidate.2HCl), DTSSP (i.e., 3,3'-dithiobis[sulfosuccinimidylpropionate])), DPDPB (i.e., 1,4-di-[3'-(2'-pyridyldithio)-propionamido]butane), and BMH (i.e., bis-maleimidohexane). Such homobifunctional cross-linkers are also available from Pierce Biotechnology, Inc.

[0155] In other instances, it may be beneficial to cleave the agent from the immunoglobulin-related composition. The web-site of Pierce Biotechnology, Inc. described above can also provide assistance to one skilled in the art in choosing suitable cross-linkers which can be cleaved by, for example, enzymes in the cell. Thus the agent can be separated from the immunoglobulin-related composition. Examples of cleavable linkers include SMPT (i.e., 4-succinimidyloxycarbonyl-methyl-a-[2-pyridyldithio]toluene), Sulfo-LC-SPDP (i.e., sulfosuccinimidyl 6-(3-[2-pyridyldithio]-propionamido)hexanoate), LC-SPDP (i.e., succinimidyl 6-(3-[2-pyridyldithio]-propionamido)hexanoate), Sulfo-LC-SPDP (i.e., sulfosuccinimidyl 6-(3-[2-pyridyldithio]-propionamido)hexanoate), SPDP (i.e., N-succinimidyl 3-[2-pyridyldithio]-propionamidohexanoate), and AEDP (i.e., 3-[(2-aminoethyl)dithio]propionic acid HCl).

[0156] In another embodiment, a conjugate comprises at least one agent physically bonded with at least one immunoglobulin-related composition. Any method known to those in the art can be employed to physically bond the agents with the immunoglobulin-related compositions. For example, the immunoglobulin-related compositions and agents can be mixed together by any method known to those in the art. The order of mixing is not important. For instance, agents can be physically mixed with immunoglobulin-related compositions by any method known to those in the art. For example, the immunoglobulin-related compositions and agents can be placed in a container and agitated, by for example, shaking the container, to mix the immunoglobulin-related compositions and agents.

[0157] The immunoglobulin-related compositions can be modified by any method known to those in the art. For instance, the immunoglobulin-related composition may be modified by means of cross-linking agents or functional groups, as described above.

[0158] Heterodimerization. The present technology is dependent on heterodimerization of two IgG-scFv half-molecules through mutations in the heterodimerization domains using techniques known in the art. Any heterodimerization approach where the hinge domain is kept in place may be employed, provided that sufficient antibody stability is achieved.

[0159] Heterodimerization of CH2-CH3 domains. Formation of a heterodimeric trivalent/tetravalent multispecific antibody molecule of the present technology requires the interaction of four different polypeptide chains. Such interactions are difficult to achieve with efficiency within a single cell recombinant production system, due to the many variants of potential chain mispairings. One solution to increase

the probability of mispairings, is to engineer "knobs-into-holes" type mutations into the desired polypeptide chain pairs. Such mutations favor heterodimerization over homodimerization. For example, with respect to Fc-Fc-interactions, an amino acid substitution (preferably a substitution with an amino acid comprising a bulky side group forming a 'knob', e.g., tryptophan) can be introduced into the CH2 or CH3 domain such that steric interference will prevent interaction with a similarly mutated domain and will obligate the mutated domain to pair with a domain into which a complementary, or accommodating mutation has been engineered, i.e., 'the hole' (e.g., a substitution with glycine). Such sets of mutations can be engineered into a pair of polypeptides that are included within the heterodimeric trivalent/tetravalent molecule (e.g., the second polypeptide chain and the third polypeptide chain), and further, engineered into any portion of the polypeptides chains of said pair. Methods of protein engineering to favor heterodimerization over homodimerization are well known in the art, in particular with respect to the engineering of immunoglobulin-like molecules, and are encompassed herein (see e.g., Ridgway et al., 1996, *Protein Engr.* 9:617-621, Atwell et al., 1997, *J. Mol. Biol.* 270: 26-35, and Xie et al., 2005, *J. Immunol. Methods* 296:95-101; each of which is hereby incorporated herein by reference in its entirety).

[0160] The design of variant Fc heterodimers from wild-type homodimers is illustrated by the concept of positive and negative design in the context of protein engineering by balancing stability vs. specificity, where mutations are introduced with the goal of driving heterodimer formation over homodimer formation when the polypeptides are expressed in cell culture conditions. Negative design strategies maximize unfavorable interactions for the formation of homodimers, by either introducing bulky sidechains on one chain and small sidechains on the opposite, for example the knobs-into-holes strategy developed by Genentech (Ridgway J B, Presta L G, Carter P. *Protein Eng.* 1996 July; 9(7):617-21; Atwell S, Ridgway J B, Wells J A, Carter P. *J Mol. Biol.* 270(1):26-35 (1997))), or by electrostatic engineering that leads to repulsion of homodimer formation, for example the electrostatic steering strategy developed by Amgen (Gunaskekaran K, et al. *JBC* 285 (25): 19637-19646 (2010)). In these two examples, negative design asymmetric point mutations are introduced into the wild-type CH3 domain to drive heterodimer formation. Other heterodimerization approaches are described in US 20120149876 (e.g., at Tables 1, 6 and 7), and US 20140294836 (e.g., at FIGS. **15**A-B, **16**A-B, and **17**). Methods for engineering Fc heterodimers using electrostatic steering are described in detail in U.S. Pat. No. 8,592,562.

[0161] In some embodiments of the HDTVS antibodies disclosed herein, the second polypeptide chain and the third polypeptide chain comprise a first CH2-CH3 domain and a second CH2-CH3 domain respectively, wherein the first CH2-CH3 domain and the second CH2-CH3 domain comprise amino acid modifications selected from the group consisting of: T366Y and Y407T respectively; F405A and T394W respectively; Y349C/T366S/L368A/Y407V and S354C/T366W respectively; K409D/K392D and D399K respectively; T366S/L368A/Y407V and T366W respectively; K409D/K392D and D399K/E356K respectively; L351Y/Y407A and T366A/K409F respectively; L351Y/Y407A and T366V/K409F respectively; Y407A and T366A/K409F respectively; D399R/S400R/Y407A and T366A/K409F/K392E/T411E respectively; L351Y/F405A/Y407V and T394W respectively; L351Y/F405A/Y407V and T366L respectively; F405A/Y407V and T366I/K392M/T394W respectively; F405A/Y407V and T366L/K392M/T394W respectively; F405A/Y407V and T366L/T394W respectively; F405A/Y407V and T366I/T394W respectively; and K409R and F405L respectively.

[0162] In some embodiments of the HDTVS antibodies disclosed herein, the second polypeptide chain and the third polypeptide chain comprise a first CH2-CH3 domain and a second CH2-CH3 domain respectively, wherein the first CH2-CH3 domain comprises an amino acid modification at position F405 and amino acid modifications L351Y and Y407V, and the second CH2-CH3 domain comprises amino acid modification T394W. In some embodiments, the amino acid modification at position F405 is F405A, F4051, F405M, F405T, F4055, F405V or F405W.

[0163] In some embodiments of the HDTVS antibodies disclosed herein, the second polypeptide chain and the third polypeptide chain comprise a first CH2-CH3 domain and a second CH2-CH3 domain respectively, wherein the first CH2-CH3 domain comprises amino acid modifications at positions L351 and Y407, and the second CH2-CH3 domain comprises an amino acid modification at position T366 and amino acid modification K409F. In some embodiments, the amino acid modification at position L351 is L351Y, L3511, L351D, L351R or L351F. In some embodiments, the amino acid modification at position Y407 is Y407A, Y407V or Y4075. In certain embodiments, the amino acid modification at position T366 is T366A, T366I, T366L, T366M, T366Y, T366S, T366C, T366V or T366W.

[0164] In some embodiments of the HDTVS antibodies disclosed herein, the second polypeptide chain and the third polypeptide chain comprise a first CH2-CH3 domain and a second CH2-CH3 domain respectively, wherein the first CH2-CH3 domain or the second CH2-CH3 domain comprises an amino acid modification at positions K392, T411, T366, L368 or 5400. The amino acid modification at position K392 may be K392V, K392M, K392R, K392L, K392F or K392E. The amino acid modification at position T411 may be T411N, T411R, T411Q, T411K, T411D, T411E or T411W. The amino acid modification at position 5400 may be S400E, 5400D, 5400R or S400K. The amino acid modification at position T366 may be T366A, T366I, T366L, T366M, T366Y, T366S, T366C, T366V or T366W. The amino acid modification at position L368 may be L368D, L368R, L368T, L368M, L368V, L368F, L368S and L368A.

[0165] In some embodiments of the HDTVS antibodies disclosed herein, the second polypeptide chain and the third polypeptide chain comprise a first CH2-CH3 domain and a second CH2-CH3 domain respectively, wherein the first CH2-CH3 domain comprises amino acid modifications L351Y and Y407A and the second CH2-CH3 domain comprises amino acid modifications T366A and K409F, and optionally wherein the first CH2-CH3 domain or the second CH2-CH3 domain comprises one or more amino acid modifications at position T411, D399, 5400, F405, N390, or K392. The amino acid modification at position T411 may be T411N, T411R, T411Q, T411K, T411D, T411E or T411W. The amino acid modification at position D399 may be D399R, D399W, D399Y or D399K. The amino acid modification at position 5400 may be S400E, 5400D, 5400R, or S400K. The amino acid modification at position F405 may be F4051, F405M, F405T, F4055, F405V or F405W. The

amino acid modification at position N390 may be N390R, N390K or N390D. The amino acid modification at position K392 may be K392V, K392M, K392R, K392L, K392F or K392E.

[0166] In some embodiments of the HDTVS antibodies disclosed herein, the second polypeptide chain and the third polypeptide chain comprise a first CH2-CH3 domain and a second CH2-CH3 domain respectively, wherein the first CH2-CH3 domain and the second CH2-CH3 domain comprise a set of amino acid modifications as shown in FIG. **11***a*. In some embodiments of the HDTVS antibodies disclosed herein, the second polypeptide chain and the third polypeptide chain comprise a first CH2-CH3 domain and a second CH2-CH3 domain respectively, wherein the first CH2-CH3 domain and the second CH2-CH3 domain comprise a set of amino acid modifications as shown in FIG. **11***b*. In some embodiments of the HDTVS antibodies disclosed herein, the second polypeptide chain and the third polypeptide chain comprise a first CH2-CH3 domain and a second CH2-CH3 domain respectively, wherein the first CH2-CH3 domain and the second CH2-CH3 domain comprise a set of amino acid modifications as shown in FIG. **11***c*. In some embodiments of the HDTVS antibodies disclosed herein, the second polypeptide chain and the third polypeptide chain comprise a first CH2-CH3 domain and a second CH2-CH3 domain respectively, wherein the first CH2-CH3 domain and the second CH2-CH3 domain comprise a set of amino acid modifications as shown in FIG. **11***d*. In some embodiments of the HDTVS antibodies disclosed herein, the second polypeptide chain and the third polypeptide chain comprise a first CH2-CH3 domain and a second CH2-CH3 domain respectively, wherein the first CH2-CH3 domain and the second CH2-CH3 domain comprise a set of amino acid modifications as shown in FIG. **11***e*.

[0167] Other Fc Modifications. In some embodiments, the heterodimeric trivalent/tetravalent multispecific antibodies of the present technology comprise a variant Fc region, wherein said variant Fc region comprises at least one amino acid modification relative to a wild-type Fc region (or the parental Fc region), such that said molecule has an altered affinity for an Fc receptor (e.g., an FcγR), provided that said variant Fc region does not have a substitution at positions that make a direct contact with Fc receptor based on crystallographic and structural analysis of Fc-Fc receptor interactions such as those disclosed by Sondermann et al., *Nature,* 406:267-273 (2000). Examples of positions within the Fc region that make a direct contact with an Fc receptor such as an FcγR, include amino acids 234-239 (hinge region), amino acids 265-269 (B/C loop), amino acids 297-299 (C7E loop), and amino acids 327-332 (F/G) loop.

[0168] In some embodiments, a heterodimeric trivalent/tetravalent multispecific antibody of the present technology has an altered affinity for activating and/or inhibitory receptors, and includes a variant Fc region with one or more amino acid modifications, wherein said one or more amino acid modification is a N297 substitution with alanine, or a K322 substitution with alanine.

[0169] Glycosylation Modifications. In some embodiments, heterodimeric trivalent/tetravalent multispecific antibodies of the present technology have an Fc region with variant glycosylation as compared to a parent Fc region. In some embodiments, variant glycosylation includes the absence of fucose; in some embodiments, variant glycosylation results from expression in GnT1-deficient CHO cells.

[0170] In some embodiments, the antibodies of the present technology, may have a modified glycosylation site relative to an appropriate reference antibody that binds to an antigen of interest, without altering the functionality of the antibody, e.g., binding activity to the antigen. As used herein, "glycosylation sites" include any specific amino acid sequence in an antibody to which an oligosaccharide (i.e., carbohydrates containing two or more simple sugars linked together) will specifically and covalently attach.

[0171] Oligosaccharide side chains are typically linked to the backbone of an antibody via either N- or O-linkages. N-linked glycosylation refers to the attachment of an oligosaccharide moiety to the side chain of an asparagine residue. O-linked glycosylation refers to the attachment of an oligosaccharide moiety to a hydroxyamino acid, e.g., serine, threonine. For example, an Fc-glycoform that lacks certain oligosaccharides including fucose and terminal N-acetylglucosamine may be produced in special CHO cells and exhibit enhanced ADCC effector function.

[0172] In some embodiments, the carbohydrate content of an immunoglobulin-related composition disclosed herein is modified by adding or deleting a glycosylation site. Methods for modifying the carbohydrate content of antibodies are well known in the art and are included within the present technology, see, e.g., U.S. Pat. No. 6,218,149; EP 0359096B1; U.S. Patent Publication No. US 2002/0028486; International Patent Application Publication WO 03/035835; U.S. Patent Publication No. 2003/0115614; U.S. Pat. Nos. 6,218,149; 6,472,511; all of which are incorporated herein by reference in their entirety. In some embodiments, the carbohydrate content of an antibody (or relevant portion or component thereof) is modified by deleting one or more endogenous carbohydrate moieties of the antibody. In certain embodiments, the present technology includes deleting the glycosylation site of the Fc region of an antibody, by modifying position 297 from asparagine to alanine. Such antibodies lack Fc effector function. In some embodiments, nonspecific FcR-dependent binding in normal tissues is eliminated or reduced (e.g., via N297A mutation in Fc region, which results in aglycosylation).

[0173] Engineered glycoforms may be useful for a variety of purposes, including but not limited to enhancing or reducing effector function. Engineered glycoforms may be generated by any method known to one skilled in the art, for example by using engineered or variant expression strains, by co-expression with one or more enzymes, for example DI N-acetylglucosaminyltransferase III (GnTIII), by expressing a molecule comprising an Fc region in various organisms or cell lines from various organisms, or by modifying carbohydrate(s) after the molecule comprising Fc region has been expressed. Methods for generating engineered glycoforms are known in the art, and include but are not limited to those described in Umana et al., 1999, *Nat. Biotechnol.* 17: 176-180; Davies et al., 2001, *Biotechnol. Bioeng.* 74:288-294; Shields et al., 2002, 1 *Biol. Chem.* 277:26733-26740; Shinkawa et al., 2003, *J Biol. Chem.* 278:3466-3473; U.S. Pat. No. 6,602,684; U.S. patent application Ser. No. 10/277,370; U.S. patent application Ser. No. 10/113,929; International Patent Application Publications WO 00/61739A1; WO 01/292246A1; WO 02/311140A1; WO 02/30954A1; POTILLEGENT™ technology (Biowa, Inc. Princeton, N.J.); GLYCOMAB™ glycosylation engineering technology (GLYCART biotechnology AG, Zurich, Switzerland); each of which is incorporated herein by reference in its

entirety. See, e.g., International Patent Application Publication WO 00/061739; U.S. Patent Application Publication No. 2003/0115614; Okazaki et al., 2004, *JMB,* 336: 1239-49.

A. Methods of Preparing Heterodimeric Trivalent/Tetravalent Multispecific Antibodies of the Present Technology

[0174] General Overview. The heterodimeric trivalent/tetravalent multispecific antibodies of the present disclosure can be produced using a variety of methods well known in the art, including de novo protein synthesis and recombinant expression of nucleic acids encoding the binding proteins. Initially, a target antigen is chosen to which an antibody of the present technology can be raised. For example, in some embodiments, an antibody may be raised against a full-length target protein, or to a portion of the target protein. Techniques for generating antibodies directed to such target polypeptides are well known to those skilled in the art. Examples of such techniques include, for example, but are not limited to, those involving display libraries, xeno or human mice, hybridomas, and the like.

[0175] Generally, an antibody is obtained from an originating species. More particularly, the nucleic acid or amino acid sequence of the variable portion of the light chain, heavy chain or both, of an originating species antibody having specificity for a target antigen is obtained. An originating species is any species which was useful to generate the antibody of the present technology or library of antibodies, e.g., rat, mouse, rabbit, chicken, monkey, human, and the like.

[0176] Phage or phagemid display technologies are useful techniques to derive the antibodies of the present technology. Techniques for generating and cloning monoclonal antibodies are well known to those skilled in the art. Expression of sequences encoding antibodies of the present technology, can be carried out in *E. coli.*

[0177] Due to the degeneracy of nucleic acid coding sequences, other sequences which encode substantially the same amino acid sequences as those of the naturally occurring proteins may be used in the practice of the present technology. These include, but are not limited to, nucleic acid sequences including all or portions of the nucleic acid sequences encoding the above polypeptides, which are altered by the substitution of different codons that encode a functionally equivalent amino acid residue within the sequence, thus producing a silent change. It is appreciated that the nucleotide sequence of an immunoglobulin according to the present technology tolerates sequence homology variations of up to 25% as calculated by standard methods ("Current Methods in Sequence Comparison and Analysis," *Macromolecule Sequencing and Synthesis, Selected Methods and Applications*, pp. 127-149, 1998, Alan R. Liss, Inc.) so long as such a variant yields an operative antibody which recognizes a target of interest. For example, one or more amino acid residues within a polypeptide sequence can be substituted by another amino acid of a similar polarity which acts as a functional equivalent, resulting in a silent alteration. Substitutes for an amino acid within the sequence may be selected from other members of the class to which the amino acid belongs. For example, the nonpolar (hydrophobic) amino acids include alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan and methionine. The polar neutral amino acids include glycine, serine, threonine, cysteine, tyrosine, asparagine, and glutamine. The positively charged (basic) amino acids include arginine, lysine and histidine. The negatively charged (acidic) amino acids include aspartic acid and glutamic acid. Also included within the scope of the present technology are proteins or fragments or derivatives thereof which are differentially modified during or after translation, e.g., by glycosylation, proteolytic cleavage, linkage to an antibody molecule or other cellular ligands, etc. Additionally, an immunoglobulin encoding nucleic acid sequence can be mutated in vitro or in vivo to create and/or destroy translation, initiation, and/or termination sequences or to create variations in coding regions and/or form new restriction endonuclease sites or destroy pre-existing ones, to facilitate further in vitro modification. Any technique for mutagenesis known in the art can be used, including but not limited to in vitro site directed mutagenesis, J. Biol. Chem. 253:6551, use of Tab linkers (Pharmacia), and the like.

[0178] Monoclonal Antibody. In one embodiment of the present technology, the heterodimeric trivalent/tetravalent multispecific antibody is a monoclonal antibody. For example, in some embodiments, the heterodimeric trivalent/tetravalent multispecific monoclonal antibody may be a human or a mouse heterodimeric trivalent/tetravalent multispecific monoclonal antibody. For preparation of monoclonal antibodies directed towards a target molecule of interest, any technique that provides for the production of antibody molecules by continuous cell line culture can be utilized. Such techniques include, but are not limited to, the hybridoma technique (See, e.g., Kohler & Milstein, 1975. Nature 256: 495-497); the trioma technique; the human B-cell hybridoma technique (See, e.g., Kozbor, et al., 1983. *Immunol. Today* 4: 72) and the EBV hybridoma technique to produce human monoclonal antibodies (See, e.g., Cole, et al., 1985. In: MONOCLONAL ANTIBODIES AND CANCER THERAPY, Alan R. Liss, Inc., pp. 77-96). Human monoclonal antibodies can be utilized in the practice of the present technology and can be produced by using human hybridomas (See, e.g., Cote, et al., 1983. *Proc. Natl. Acad. Sci*. USA 80: 2026-2030) or by transforming human B-cells with Epstein Barr Virus in vitro (See, e.g., Cole, et al., 1985. In: MONOCLONAL ANTIBODIES AND CANCER THERAPY, Alan R. Liss, Inc., pp. 77-96). For example, a population of nucleic acids that encode regions of antibodies can be isolated. PCR utilizing primers derived from sequences encoding conserved regions of antibodies is used to amplify sequences encoding portions of antibodies from the population and then DNAs encoding polypeptide chains of the heterodimeric trivalent/tetravalent multispecific antibodies or fragments thereof, such as variable domains, are reconstructed from the amplified sequences. Such amplified sequences also can be fused to DNAs encoding other proteins—e.g., a bacteriophage coat, or a bacterial cell surface protein—for expression and display of the fusion polypeptides on phage or bacteria. Amplified sequences can then be expressed and further selected or isolated based, e.g., on the affinity of the expressed antibody or fragment thereof for an antigen or epitope present on the target molecule of interest. Alternatively, hybridomas expressing heterodimeric trivalent/tetravalent multispecific monoclonal antibodies can be prepared by immunizing a subject and then isolating hybridomas from the subject's spleen using routine methods. See, e.g., Milstein et al., (Galfre and Milstein, *Methods Enzymol* (1981) 73: 3-46). Screening the hybridomas using

standard methods will produce monoclonal antibodies of varying specificity (i.e., for different epitopes) and affinity. A selected monoclonal antibody with the desired properties, e.g., binding to a target antigen, can be used as expressed by the hybridoma, it can be bound to a molecule such as polyethylene glycol (PEG) to alter its properties, or a cDNA encoding it can be isolated, sequenced and manipulated in various ways. Synthetic dendromeric trees can be added to reactive amino acid side chains, e.g., lysine, to enhance the immunogenic properties of a target protein. Also, CPG-dinucleotide techniques can be used to enhance the immunogenic properties of the target protein. Other manipulations include substituting or deleting particular amino acyl residues that contribute to instability of the antibody during storage or after administration to a subject, and affinity maturation techniques to improve affinity of the antibody towards its target antigen.

[0179] Hybridoma Technique. In some embodiments, the antibody of the present technology is a heterodimeric trivalent/tetravalent multispecific monoclonal antibody produced by a hybridoma which includes a B cell obtained from a transgenic non-human animal, e.g., a transgenic mouse, having a genome comprising a human heavy chain transgene and a light chain transgene fused to an immortalized cell. Hybridoma techniques include those known in the art and taught in Harlow et al., *Antibodies: A Laboratory Manual* Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y., 349 (1988); Hammerling et al., *Monoclonal Antibodies And T-Cell Hybridomas,* 563-681 (1981). Other methods for producing hybridomas and monoclonal antibodies are well known to those of skill in the art.

[0180] Phage Display Technique. As noted above, the antibodies of the present technology can be produced through the application of recombinant DNA and phage display technology. For example, heterodimeric trivalent/tetravalent multi specific antibodies, can be prepared using various phage display methods known in the art. In phage display methods, functional antibody domains are displayed on the surface of a phage particle which carries polynucleotide sequences encoding them. Phages with a desired binding property are selected from a repertoire or combinatorial antibody library (e.g., human or murine) by selecting directly with an antigen, typically an antigen bound or captured to a solid surface or bead. Phages used in these methods are typically filamentous phage including fd and M13 with Fab, Fv or disulfide stabilized Fv antibody domains that are recombinantly fused to either the phage gene III or gene VIII protein. In addition, methods can be adapted for the construction of Fab expression libraries (See, e.g., Huse, et al., *Science* 246: 1275-1281, 1989) to allow rapid and effective identification of monoclonal Fab fragments with the desired specificity for a target antigen, e.g., a target polypeptide or derivatives, fragments, analogs or homologs thereof. Other examples of phage display methods that can be used to make the antibodies of the present technology include those disclosed in Huston et al., *Proc. Natl. Acad. Sci U.S.A.,* 85: 5879-5883, 1988; Chaudhary et al., *Proc. Natl. Acad. Sci U.S.A.,* 87: 1066-1070, 1990; Brinkman et al., *J. Immunol. Methods* 182: 41-50, 1995; Ames et al., *J. Immunol. Methods* 184: 177-186, 1995; Kettleborough et al., *Eur. J Immunol.* 24: 952-958, 1994; Persic et al., *Gene* 187: 9-18, 1997; Burton et al., *Advances in Immunology* 57: 191-280, 1994; PCT/GB91/01134; WO 90/02809; WO 91/10737; WO 92/01047; WO 92/18619; WO 93/11236; WO 95/15982; WO 95/20401; WO 96/06213; WO 92/01047 (Medical Research Council et al.); WO 97/08320 (Morphosys); WO 92/01047 (CAT/MRC); WO 91/17271 (Affymax); and U.S. Pat. Nos. 5,698,426, 5,223,409, 5,403,484, 5,580,717, 5,427,908, 5,750,753, 5,821,047, 5,571,698, 5,427,908, 5,516,637, 5,780,225, 5,658,727 and 5,733,743. Methods useful for displaying polypeptides on the surface of bacteriophage particles by attaching the polypeptides via disulfide bonds have been described by Lohning, U.S. Pat. No. 6,753,136. As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate whole antibodies, including human antibodies, or any other desired antigen binding fragment, and expressed in any desired host including mammalian cells, insect cells, plant cells, yeast, and bacteria. For example, techniques to recombinantly produce Fab, Fab' and $F(ab')_2$ fragments can also be employed using methods known in the art such as those disclosed in WO 92/22324; Mullinax et al., *BioTechniques* 12: 864-869, 1992; and Sawai et al., *AJRI* 34: 26-34, 1995; and Better et al., *Science* 240: 1041-1043, 1988.

[0181] Generally, hybrid antibodies or hybrid antibody fragments that are cloned into a display vector can be selected against the appropriate antigen in order to identify variants that maintain good binding activity, because the antibody or antibody fragment will be present on the surface of the phage or phagemid particle. See, e.g., Barbas III et al., *Phage Display, A Laboratory Manual* (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 2001). However, other vector formats could be used for this process, such as cloning the antibody fragment library into a lytic phage vector (modified T7 or Lambda Zap systems) for selection and/or screening.

[0182] Single-Chain Fvs. The heterodimeric trivalent/tetravalent multispecific antibody of the present technology comprises two single-chain Fvs. According to the present technology, techniques can be adapted for the production of single-chain antibodies specific to a target antigen (See, e.g., U.S. Pat. No. 4,946,778). Examples of techniques which can be used to produce single-chain Fvs and antibodies of the present technology include those described in U.S. Pat. Nos. 4,946,778 and 5,258,498; Huston et al., *Methods in Enzymology,* 203: 46-88, 1991; Shu, L. et al., *Proc. Natl. Acad. Sci*. USA, 90: 7995-7999, 1993; and Skerra et al., *Science* 240: 1038-1040, 1988.

[0183] Chimeric and Humanized Antibodies. In one embodiment, the heterodimeric trivalent/tetravalent multispecific antibody of the present technology is chimeric. In one embodiment, the heterodimeric trivalent/tetravalent multispecific antibody of the present technology is humanized. In one embodiment of the present technology, the donor and acceptor antibodies are monoclonal antibodies from different species. For example, the acceptor antibody is a human antibody (to minimize its antigenicity in a human), in which case the resulting CDR-grafted antibody is termed a "humanized" antibody.

[0184] Recombinant heterodimeric trivalent/tetravalent multispecific antibodies, such as chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, can be made using standard recombinant DNA techniques, and are within the scope of the present technology. For some uses, including in vivo use of the heterodimeric trivalent/tetravalent multispecific antibody of the present technology in humans as well as use of these

agents in in vitro detection assays, it is possible to use chimeric or humanized heterodimeric trivalent/tetravalent multispecific antibodies. Such chimeric and humanized monoclonal antibodies can be produced by recombinant DNA techniques known in the art. Such useful methods include, e.g., but are not limited to, methods described in International Application No. PCT/US86/02269; U.S. Pat. No. 5,225,539; European Patent No. 184187; European Patent No. 171496; European Patent No. 173494; PCT International Publication No. WO 86/01533; U.S. Pat. Nos. 4,816,567; 5,225,539; European Patent No. 125023; Better, et al., 1988. *Science* 240: 1041-1043; Liu, et al., 1987. *Proc. Natl. Acad. Sci. USA* 84: 3439-3443; Liu, et al., 1987. *J Immunol.* 139: 3521-3526; Sun, et al., 1987. *Proc. Natl. Acad. Sci. USA* 84: 214-218; Nishimura, et al., 1987. *Cancer Res.* 47: 999-1005; Wood, et al., 1985. *Nature* 314: 446-449; Shaw, et al., 1988. *J Natl. Cancer Inst.* 80: 1553-1559; Morrison (1985) *Science* 229: 1202-1207; Oi, et al. (1986) *BioTechniques* 4: 214; Jones, et al., 1986. *Nature* 321: 552-525; Verhoeyan, et al., 1988. *Science* 239: 1534; Morrison, *Science* 229: 1202, 1985; Oi et al., *BioTechniques* 4: 214, 1986; Gillies et al., *J. Immunol. Methods,* 125: 191-202, 1989; U.S. Pat. No. 5,807,715; and Beidler, et al., 1988. *J. Immunol.* 141: 4053-4060. For example, antibodies can be humanized using a variety of techniques including CDR-grafting (EP 0 239 400; WO 91/09967; U.S. Pat. Nos. 5,530,101; 5,585,089; 5,859,205; 6,248,516; EP460167), veneering or resurfacing (EP 0 592 106; EP 0 519 596; Padlan E. A., *Molecular Immunology,* 28: 489-498, 1991; Studnicka et al., *Protein Engineering* 7: 805-814, 1994; Roguska et al., *PNAS* 91: 969-973, 1994), and chain shuffling (U.S. Pat. No. 5,565,332). In one embodiment, a cDNA encoding a murine heterodimeric trivalent/tetravalent multispecific monoclonal antibody is digested with a restriction enzyme selected specifically to remove the sequence encoding the Fc constant region, and the equivalent portion of a cDNA encoding a human Fc constant region is substituted (See Robinson et al., PCT/US86/02269; Akira et al., European Patent Application 184,187; Taniguchi, European Patent Application 171,496; Morrison et al., European Patent Application 173,494; Neuberger et al., WO 86/01533; Cabilly et al. U.S. Pat. No. 4,816,567; Cabilly et al., European Patent Application 125,023; Better et al. (1988) Science 240: 1041-1043; Liu et al. (1987) *Proc. Natl. Acad. Sci.* USA 84: 3439-3443; Liu et al. (1987) *J Immunol* 139: 3521-3526; Sun et al. (1987) *Proc. Natl. Acad. Sci.* USA 84: 214-218; Nishimura et al. (1987) *Cancer Res* 47: 999-1005; Wood et al. (1985) *Nature* 314: 446-449; and Shaw et al. (1988) *J. Natl. Cancer Inst.* 80: 1553-1559; U.S. Pat. Nos. 6,180,370; 6,300,064; 6,696,248; 6,706,484; 6,828,422.

[0185] In one embodiment, the present technology provides the construction of humanized heterodimeric trivalent/tetravalent multispecific antibodies that are unlikely to induce a human anti-mouse antibody (hereinafter referred to as "HAMA") response, while still having an effective antibody effector function. As used herein, the terms "human" and "humanized", in relation to antibodies, relate to any antibody which is expected to elicit a therapeutically tolerable weak immunogenic response in a human subject. In one embodiment, the present technology provides for a humanized heterodimeric trivalent/tetravalent multispecific antibody comprising both heavy chain and light chain polypeptides.

[0186] CDR Antibodies. In some embodiments, the heterodimeric trivalent/tetravalent multispecific antibody of the present technology is a CDR antibody. Generally the donor and acceptor antibodies used to generate the heterodimeric trivalent/tetravalent multispecific CDR antibody are monoclonal antibodies from different species; typically the acceptor antibody is a human antibody (to minimize its antigenicity in a human), in which case the resulting CDR-grafted antibody is termed a "humanized" antibody. The graft may be of a single CDR (or even a portion of a single CDR) within a single V_H or V_L of the acceptor antibody, or can be of multiple CDRs (or portions thereof) within one or both of the V_H and V_L. Frequently, all three CDRs in all variable domains of the acceptor antibody will be replaced with the corresponding donor CDRs, though one need replace only as many as necessary to permit adequate binding of the resulting CDR-grafted antibody to the target antigen. Methods for generating CDR-grafted and humanized antibodies are taught by Queen et al. U.S. Pat. Nos. 5,585,089; 5,693,761; 5,693,762; and Winter U.S. Pat. No. 5,225,539; and EP 0682040. Methods useful to prepare V_H and V_L polypeptides are taught by Winter et al., U.S. Pat. Nos. 4,816,397; 6,291,158; 6,291,159; 6,291,161; 6,545,142; EP 0368684; EP0451216; and EP0120694.

[0187] After selecting suitable framework region candidates from the same family and/or the same family member, either or both the heavy and light chain variable regions are produced by grafting the CDRs from the originating species into the hybrid framework regions. Assembly of hybrid antibodies or hybrid antibody fragments having hybrid variable chain regions with regard to either of the above aspects can be accomplished using conventional methods known to those skilled in the art. For example, DNA sequences encoding the hybrid variable domains described herein (i.e., frameworks based on the target species and CDRs from the originating species) can be produced by oligonucleotide synthesis and/or PCR. The nucleic acid encoding CDR regions can also be isolated from the originating species antibodies using suitable restriction enzymes and ligated into the target species framework by ligating with suitable ligation enzymes. Alternatively, the framework regions of the variable chains of the originating species antibody can be changed by site-directed mutagenesis.

[0188] Since the hybrids are constructed from choices among multiple candidates corresponding to each framework region, there exist many combinations of sequences which are amenable to construction in accordance with the principles described herein. Accordingly, libraries of hybrids can be assembled having members with different combinations of individual framework regions. Such libraries can be electronic database collections of sequences or physical collections of hybrids.

[0189] This process typically does not alter the acceptor antibody's FRs flanking the grafted CDRs. However, one skilled in the art can sometimes improve antigen binding affinity of the resulting heterodimeric trivalent/tetravalent multispecific CDR-grafted antibody by replacing certain residues of a given FR to make the FR more similar to the corresponding FR of the donor antibody. Suitable locations of the substitutions include amino acid residues adjacent to the CDR, or which are capable of interacting with a CDR (See, e.g., U.S. Pat. No. 5,585,089, especially columns 12-16). Or one skilled in the art can start with the donor FR and modify it to be more similar to the acceptor FR or a

human consensus FR. Techniques for making these modifications are known in the art. Particularly if the resulting FR fits a human consensus FR for that position, or is at least 90% or more identical to such a consensus FR, doing so may not increase the antigenicity of the resulting modified heterodimeric trivalent/tetravalent multispecific CDR-grafted antibody significantly compared to the same antibody with a fully human FR.

[0190] Expression of Recombinant Heterodimeric Trivalent/Tetravalent Multispecific Antibodies. The desired nucleic acid sequences can be produced by recombinant methods (e.g., PCR mutagenesis of an earlier prepared variant of the desired polynucleotide) or by solid-phase DNA synthesis. Because of the degeneracy of the genetic code, a variety of nucleic acid sequences encode each immunoglobulin amino acid sequence, and the present disclosure includes all nucleic acids encoding the binding proteins described herein, which are suitable for use in accordance with the present disclosure.

[0191] Once the nucleotide sequence of the heterodimeric trivalent/tetravalent multispecific antibodies are determined, the nucleotide sequence may be manipulated using methods well known in the art, e.g., recombinant DNA techniques, site directed mutagenesis, PCR, etc. (see, for example, the techniques described in Sambrook et al., 2001, *Molecular Cloning, A Laboratory Manual,* 3rd Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y.; and Ausubel et al., eds., 1998, *Current Protocols in Molecular Biology*, John Wiley & Sons, NY, which are both incorporated by reference herein in their entireties), to generate, for example, antibodies having a different amino acid sequence, for example by generating amino acid substitutions, deletions, and/or insertions. In one embodiment, human libraries or any other libraries available in the art, can be screened by standard techniques known in the art, to clone the nucleic acids encoding the heterodimeric trivalent/tetravalent multispecific antibodies of the present disclosure.

[0192] As noted above, the antibodies of the present technology can be produced through the application of recombinant DNA technology. Recombinant polynucleotide constructs encoding a heterodimeric trivalent/tetravalent multispecific antibody of the present technology typically include an expression control sequence operably-linked to the coding sequences of heterodimeric trivalent/tetravalent multispecific antibody chains, including naturally-associated or heterologous promoter regions. As such, another aspect of the technology includes vectors containing one or more nucleic acid sequences encoding a heterodimeric trivalent/tetravalent multispecific antibody of the present technology. Methods which are well known to those skilled in the art can be used to construct expression vectors containing the coding sequences for the molecules of the present disclosure and appropriate transcriptional and translational control signals. These methods include, for example, in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. See, for example, the techniques described in Sambrook et al., 1990, *Molecular Cloning, A Laboratory Manual,* 2d Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y. and Ausubel et al. eds., 1998, *Current Protocols in Molecular Biology*, John Wiley & Sons, NY. For recombinant expression of one or more of the polypeptides of the present technology, the nucleic acid containing all or a portion of the nucleotide sequence encoding the heterodimeric trivalent/tetravalent multispecific antibody is inserted into an appropriate cloning vector, or an expression vector (i.e., a vector that contains the necessary elements for the transcription and translation of the inserted polypeptide coding sequence) by recombinant DNA techniques well known in the art and as detailed below. Methods for producing diverse populations of vectors have been described by Lerner et al., U.S. Pat. Nos. 6,291,160 and 6,680,192.

[0193] In general, expression vectors useful in recombinant DNA techniques are often in the form of plasmids. In the present disclosure, "plasmid" and "vector" can be used interchangeably as the plasmid is the most commonly used form of vector. However, the present technology is intended to include such other forms of expression vectors that are not technically plasmids, such as viral vectors (e.g., replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions. Such viral vectors permit infection of a subject and expression of a construct in that subject. In some embodiments, the expression control sequences are eukaryotic promoter systems in vectors capable of transforming or transfecting eukaryotic host cells. Once the vector has been incorporated into the appropriate host, the host is maintained under conditions suitable for high level expression of the nucleotide sequences encoding the heterodimeric trivalent/tetravalent multispecific antibody, and the collection and purification of the heterodimeric trivalent/tetravalent multispecific antibody, e.g., cross-reacting heterodimeric trivalent/tetravalent multispecific antibodies. See generally, U.S. 2002/0199213. These expression vectors are typically replicable in the host organisms either as episomes or as an integral part of the host chromosomal DNA. Commonly, expression vectors contain selection markers, e.g., ampicillin-resistance or hygromycin-resistance, to permit detection of those cells transformed with the desired DNA sequences. Vectors can also encode signal peptide, e.g., pectate lyase, useful to direct the secretion of extracellular antibody fragments. See U.S. Pat. No. 5,576,195.

[0194] The recombinant expression vectors of the present technology comprise a nucleic acid encoding a protein having binding properties to a molecule of interest and in a form suitable for expression of the nucleic acid in a host cell, which means that the recombinant expression vectors include one or more regulatory sequences, selected on the basis of the host cells to be used for expression that is operably-linked to the nucleic acid sequence to be expressed. Within a recombinant expression vector, "operably-linked" is intended to mean that the nucleotide sequence of interest is linked to the regulatory sequence(s) in a manner that allows for expression of the nucleotide sequence (e.g., in an in vitro transcription/translation system or in a host cell when the vector is introduced into the host cell). The term "regulatory sequence" is intended to include promoters, enhancers and other expression control elements (e.g., polyadenylation signals). Such regulatory sequences are described, e.g., in Goeddel, GENE EXPRESSION TECHNOLOGY: METHODS IN ENZYMOLOGY 185, Academic Press, San Diego, Calif. (1990). Regulatory sequences include those that direct constitutive expression of a nucleotide sequence in many types of host cell and those that direct expression of the nucleotide sequence only in certain host cells (e.g., tissue-specific regulatory sequences) or under certain environmental conditions (e.g., inducible regulatory sequences). It will be appreciated by those skilled

in the art that the design of the expression vector can depend on such factors as the choice of the host cell to be transformed, the level of expression of polypeptide desired, etc. Typical regulatory sequences useful as promoters of recombinant polypeptide expression (e.g., a heterodimeric trivalent/tetravalent multispecific antibody), include, e.g., but are not limited to, promoters of 3-phosphoglycerate kinase and other glycolytic enzymes. Inducible yeast promoters include, among others, promoters from alcohol dehydrogenase, isocytochrome C, and enzymes responsible for maltose and galactose utilization. In one embodiment, a polynucleotide encoding a heterodimeric trivalent/tetravalent multispecific antibody of the present technology is operably-linked to an ara B promoter and expressible in a host cell. See U.S. Pat. No. 5,028,530. The expression vectors of the present technology can be introduced into host cells to thereby produce polypeptides or peptides, including fusion polypeptides, encoded by nucleic acids as described herein (e.g., heterodimeric trivalent/tetravalent multispecific antibody, etc.).

[0195] Another aspect of the present technology pertains to heterodimeric trivalent/tetravalent multispecific antibody-expressing host cells, which contain a nucleic acid encoding one or more heterodimeric trivalent/tetravalent multispecific antibodies. A variety of host-expression vector systems may be utilized to express the heterodimeric trivalent/tetravalent multispecific antibodies of the present disclosure. Such host-expression systems represent vehicles by which the coding sequences of the heterodimeric trivalent/tetravalent multispecific antibodies of the present disclosure may be produced and subsequently purified, but also represent cells which may, when transformed or transfected with the appropriate nucleotide coding sequences, express the molecules of the present disclosure in situ. These include, but are not limited to, microorganisms such as bacteria (e.g., *E. coli* and *B. subtilis*) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA, expression vectors containing coding sequences for the heterodimeric trivalent/tetravalent multispecific antibodies of the present disclosure; yeast (e.g., *Saccharomyces Pichia*) transformed with recombinant yeast expression vectors containing sequences encoding the heterodimeric trivalent/tetravalent multispecific antibodies of the present disclosure; insect cell systems infected with recombinant virus expression vectors (e.g., baculovirus) containing the sequences encoding the heterodimeric trivalent/tetravalent multispecific antibodies of the present disclosure; plant cell systems infected with recombinant virus expression vectors (e.g., cauliflower mosaic virus (CaMV) and tobacco mosaic virus (TMV) or transformed with recombinant plasmid expression vectors (e.g., Ti plasmid) containing sequences encoding the heterodimeric trivalent/tetravalent multispecific antibodies of the present disclosure; or mammalian cell systems (e.g., COS, CHO, BHK, 293, 293T, 3T3 cells, lymphotic cells (see U.S. Pat. No. 5,807,715), Per C.6 cells (human retinal cells developed by Crucell) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (e.g., metallothionein promoter) or from mammalian viruses (e.g., the adenovirus late promoter; the vaccinia virus 7.5K promoter).

[0196] The recombinant expression vectors of the present technology can be designed for expression of a heterodimeric trivalent/tetravalent multispecific antibody in prokaryotic or eukaryotic cells. For example, a heterodimeric trivalent/tetravalent multispecific antibody can be expressed in bacterial cells such as *Escherichia coli*, insect cells (using baculovirus expression vectors), fungal cells, e.g., yeast, yeast cells or mammalian cells. Suitable host cells are discussed further in Goeddel, GENE EXPRESSION TECHNOLOGY: METHODS IN ENZYMOLOGY 185, Academic Press, San Diego, Calif. (1990). Alternatively, the recombinant expression vector can be transcribed and translated in vitro, e.g., using T7 promoter regulatory sequences and T7 polymerase. Methods useful for the preparation and screening of polypeptides having a predetermined property, e.g., heterodimeric trivalent/tetravalent multispecific antibody, via expression of stochastically generated polynucleotide sequences have been previously described. See U.S. Pat. Nos. 5,763,192; 5,723,323; 5,814,476; 5,817,483; 5,824,514; 5,976,862; 6,492,107; 6,569,641.

[0197] Expression of polypeptides in prokaryotes is most often carried out in *E. coli* with vectors containing constitutive or inducible promoters directing the expression of either fusion or non-fusion polypeptides. Fusion vectors add a number of amino acids to a polypeptide encoded therein, usually to the amino terminus of the recombinant polypeptide. Such fusion vectors typically serve three purposes: (i) to increase expression of recombinant polypeptide; (ii) to increase the solubility of the recombinant polypeptide; and (iii) to aid in the purification of the recombinant polypeptide by acting as a ligand in affinity purification. Often, in fusion expression vectors, a proteolytic cleavage site is introduced at the junction of the fusion moiety and the recombinant polypeptide to enable separation of the recombinant polypeptide from the fusion moiety subsequent to purification of the fusion polypeptide. Such enzymes, and their cognate recognition sequences, include Factor Xa, thrombin and enterokinase. Typical fusion expression vectors include pGEX (Pharmacia Biotech Inc; Smith and Johnson, 1988. *Gene* 67: 31-40), pMAL (New England Biolabs, Beverly, Mass.) and pRIT5 (Pharmacia, Piscataway, N.J.) that fuse glutathione S-transferase (GST), maltose E binding polypeptide, or polypeptide A, respectively, to the target recombinant polypeptide.

[0198] Examples of suitable inducible non-fusion *E. coli* expression vectors include pTrc (Amrann et al., (1988) *Gene* 69: 301-315) and pET 11d (Studier et al., GENE EXPRESSION TECHNOLOGY: METHODS IN ENZYMOLOGY 185, Academic Press, San Diego, Calif. (1990) 60-89). Methods for targeted assembly of distinct active peptide or protein domains to yield multifunctional polypeptides via polypeptide fusion have been described by Pack et al., U.S. Pat. Nos. 6,294,353; 6,692,935. One strategy to maximize recombinant polypeptide expression, e.g., a heterodimeric trivalent/tetravalent multispecific antibody, in *E. coli* is to express the polypeptide in host bacteria with an impaired capacity to proteolytically cleave the recombinant polypeptide. See, e.g., Gottesman, GENE EXPRESSION TECHNOLOGY: METHODS IN ENZYMOLOGY 185, Academic Press, San Diego, Calif. (1990) 119-128. Another strategy is to alter the nucleic acid sequence of the nucleic acid to be inserted into an expression vector so that the individual codons for each amino acid are those preferentially utilized in the expression host, e.g., *E. coli* (See, e.g., Wada, et al., 1992. *Nucl. Acids Res.* 20: 2111-2118). Such alteration of nucleic acid sequences of the present technology can be carried out by standard DNA synthesis techniques.

[0199] In another embodiment, the heterodimeric trivalent/tetravalent multispecific antibody expression vector is a yeast expression vector. Examples of vectors for expression in yeast *Saccharomyces cerevisiae* include pYepSec1 (Baldari, et al., 1987. *EMBO J.* 6: 229-234), pMFa (Kurjan and Herskowitz, *Cell* 30: 933-943, 1982), pJRY88 (Schultz et al., *Gene* 54: 113-123, 1987), pYES2 (Invitrogen Corporation, San Diego, Calif.), and picZ (Invitrogen Corp, San Diego, Calif.). Alternatively, a heterodimeric trivalent/tetravalent multispecific antibody can be expressed in insect cells using baculovirus expression vectors. Baculovirus vectors available for expression of polypeptides, e.g., heterodimeric trivalent/tetravalent multispecific antibody, in cultured insect cells (e.g., SF9 cells) include the pAc series (Smith, et al., *Mol. Cell. Biol.* 3: 2156-2165, 1983) and the pVL series (Lucklow and Summers, 1989. *Virology* 170: 31-39).

[0200] In yet another embodiment, a nucleic acid encoding a heterodimeric trivalent/tetravalent multispecific antibody of the present technology is expressed in mammalian cells using a mammalian expression vector. Examples of mammalian expression vectors include, e.g., but are not limited to, pCDM8 (Seed, *Nature* 329: 840, 1987) and pMT2PC (Kaufman, et al., *EMBO J.* 6: 187-195, 1987). When used in mammalian cells, the expression vector's control functions are often provided by viral regulatory elements. For example, commonly used promoters are derived from polyoma, adenovirus 2, cytomegalovirus, and simian virus 40. For other suitable expression systems for both prokaryotic and eukaryotic cells that are useful for expression of the heterodimeric trivalent/tetravalent multispecific antibody of the present technology, see, e.g., Chapters 16 and 17 of Sambrook, et al., MOLECULAR CLONING: A LABORATORY MANUAL. 2nd ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989.

[0201] In another embodiment, the recombinant mammalian expression vector is capable of directing expression of the nucleic acid in a particular cell type (e.g., tissue-specific regulatory elements). Tissue-specific regulatory elements are known in the art. Non-limiting examples of suitable tissue-specific promoters include the albumin promoter (liver-specific; Pinkert, et al., *Genes Dev.* 1: 268-277, 1987), lymphoid-specific promoters (Calame and Eaton, *Adv. Immunol.* 43: 235-275, 1988), promoters of T cell receptors (Winoto and Baltimore, *EMBO J.* 8: 729-733, 1989) and immunoglobulins (Banerji, et al., 1983. *Cell* 33: 729-740; Queen and Baltimore, *Cell* 33: 741-748, 1983.), neuron-specific promoters (e.g., the neurofilament promoter; Byrne and Ruddle, *Proc. Natl. Acad. Sci.* USA 86: 5473-5477, 1989), pancreas-specific promoters (Edlund, et al., 1985. Science 230: 912-916), and mammary gland-specific promoters (e.g., milk whey promoter; U.S. Pat. No. 4,873,316 and European Application Publication No. 264,166). Developmentally-regulated promoters are also encompassed, e.g., the murine hox promoters (Kessel and Gruss, *Science* 249: 374-379, 1990) and the α-fetoprotein promoter (Campes and Tilghman, *Genes Dev.* 3: 537-546, 1989).

[0202] Another aspect of the present methods pertains to host cells into which a recombinant expression vector of the present technology has been introduced. The terms "host cell" and "recombinant host cell" are used interchangeably herein. It is understood that such terms refer not only to the particular subject cell but also to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

[0203] A host cell can be any prokaryotic or eukaryotic cell. For example, a heterodimeric trivalent/tetravalent multispecific antibody can be expressed in bacterial cells such as *E. coli*, insect cells, yeast or mammalian cells. Mammalian cells are a suitable host for expressing nucleotide segments encoding immunoglobulins or fragments thereof. See Winnacker, *From Genes To Clones*, (VCH Publishers, N Y, 1987). A number of suitable host cell lines capable of secreting intact heterologous proteins have been developed in the art, and include Chinese hamster ovary (CHO) cell lines, various COS cell lines, HeLa cells, L cells and myeloma cell lines. In some embodiments, the cells are non-human. For example, mammalian cells such as Chinese hamster ovary cells (CHO), in conjunction with a vector such as the major intermediate early gene promoter element from human cytomegalovirus can be an effective expression system for immunoglobulins (Foecking et al., 1998, *Gene* 45:101; Cockett et al., 1990, *BioTechnology* 8:2).

[0204] Expression vectors for these cells can include expression control sequences, such as an origin of replication, a promoter, an enhancer, and necessary processing information sites, such as ribosome binding sites, RNA splice sites, polyadenylation sites, and transcriptional terminator sequences. Queen et al., *Immunol. Rev.* 89: 49, 1986. Illustrative expression control sequences are promoters derived from endogenous genes, cytomegalovirus, SV40, adenovirus, bovine papillomavirus, and the like. Co et al., *J Immunol.* 148: 1149, 1992. Other suitable host cells are known to those skilled in the art.

[0205] Vector DNA can be introduced into prokaryotic or eukaryotic cells via conventional transformation or transfection techniques. As used herein, the terms "transformation" and "transfection" are intended to refer to a variety of art-recognized techniques for introducing foreign nucleic acid (e.g., DNA) into a host cell, including calcium phosphate or calcium chloride co-precipitation, DEAE-dextran-mediated transfection, lipofection, electroporation, biolistics or viral-based transfection. Other methods used to transform mammalian cells include the use of polybrene, protoplast fusion, liposomes, electroporation, and microinjection (See generally, Sambrook et al., *Molecular Cloning*). Suitable methods for transforming or transfecting host cells can be found in Sambrook, et al. (MOLECULAR CLONING: A LABORATORY MANUAL. 2nd ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989), and other laboratory manuals. The vectors containing the DNA segments of interest can be transferred into the host cell by well-known methods, depending on the type of cellular host.

[0206] For stable transfection of mammalian cells, it is known that, depending upon the expression vector and transfection technique used, only a small fraction of cells may integrate the foreign DNA into their genome. In order to identify and select these integrants, a gene that encodes a selectable marker (e.g., resistance to antibiotics) is generally introduced into the host cells along with the gene of interest. Various selectable markers include those that confer resistance to drugs, such as G418, hygromycin and methotrexate. Nucleic acid encoding a selectable marker can be introduced

into a host cell on the same vector as that encoding the heterodimeric trivalent/tetravalent multispecific antibody or can be introduced on a separate vector. Cells stably transfected with the introduced nucleic acid can be identified by drug selection (e.g., cells that have incorporated the selectable marker gene will survive, while the other cells die).

[0207] A host cell that includes a heterodimeric trivalent/tetravalent multispecific antibody of the present technology, such as a prokaryotic or eukaryotic host cell in culture, can be used to produce (i.e., express) a recombinant heterodimeric trivalent/tetravalent multispecific antibody. In one embodiment, the method comprises culturing the host cell (into which a recombinant expression vector encoding the heterodimeric trivalent/tetravalent multispecific antibody has been introduced) in a suitable medium such that the heterodimeric trivalent/tetravalent multispecific antibody is produced. In another embodiment, the method further comprises the step of isolating the heterodimeric trivalent/tetravalent multispecific antibody from the medium or the host cell. Once expressed, collections of the heterodimeric trivalent/tetravalent multispecific antibody, e.g., the heterodimeric trivalent/tetravalent multispecific antibodies or the heterodimeric trivalent/tetravalent multispecific antibody-related polypeptides are purified from culture media and host cells. The heterodimeric trivalent/tetravalent multispecific antibody can be purified according to standard procedures of the art, including HPLC purification, column chromatography, gel electrophoresis and the like. In one embodiment, the heterodimeric trivalent/tetravalent multispecific antibody is produced in a host organism by the method of Boss et al., U.S. Pat. No. 4,816,397. Usually, heterodimeric trivalent/tetravalent multispecific antibody chains are expressed with signal sequences and are thus released to the culture media. However, if the heterodimeric trivalent/tetravalent multispecific antibody chains are not naturally secreted by host cells, the heterodimeric trivalent/tetravalent multispecific antibody chains can be released by treatment with mild detergent. Purification of recombinant polypeptides is well known in the art and includes ammonium sulfate precipitation, affinity chromatography purification technique, column chromatography, ion exchange purification technique, gel electrophoresis and the like (See generally Scopes, Protein Purification (Springer-Verlag, N.Y., 1982).

[0208] Polynucleotides encoding heterodimeric trivalent/tetravalent multispecific antibodies, e.g., the heterodimeric trivalent/tetravalent multispecific antibody coding sequences, can be incorporated in transgenes for introduction into the genome of a transgenic animal and subsequent expression in the milk of the transgenic animal. See, e.g., U.S. Pat. Nos. 5,741,957, 5,304,489, and 5,849,992. Suitable transgenes include coding sequences for light and/or heavy chains in operable linkage with a promoter and enhancer from a mammary gland specific gene, such as casein or β-lactoglobulin. For production of transgenic animals, transgenes can be microinjected into fertilized oocytes, or can be incorporated into the genome of embryonic stem cells, and the nuclei of such cells transferred into enucleated oocytes.

[0209] In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the molecule being expressed. For example, when a large quantity of such a protein is to be produced, for the generation of pharmaceutical compositions of an antibody, vectors which direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited, to the *E. coli* expression vector pUR278 (Ruther et al., 1983, *EMBO J.* 2:1791), in which the antibody coding sequence may be ligated individually into the vector in frame with the lac Z coding region so that a fusion protein is produced; pIN vectors (Inouye & Inouye, 1985, *Nucleic Acids Res.* 13:3101-3109; Van Heeke & Schuster, 1989, *J. Biol. Chem.* 24:5503-5509); and the like. pGEX vectors may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption and binding to a matrix glutathione-agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

[0210] In an insect system, *Autographa californica* nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda* cells. The antibody coding sequence may be cloned individually into non-essential regions (e.g., the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (e.g., the polyhedrin promoter).

[0211] In mammalian host cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, the antibody coding sequence of interest may be ligated to an adenovirus transcription/translation control complex, e.g., the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by in vitro or in vivo recombination. Insertion in a non-essential region of the viral genome (e.g., region E1 or E3) will result in a recombinant virus that is viable and capable of expressing the immunoglobulin molecule in infected hosts (e.g., see Logan & Shenk, 1984, *Proc. Natl. Acad. Sci.* USA 81:355-359). Specific initiation signals may also be required for efficient translation of inserted antibody coding sequences. These signals include the ATG initiation codon and adjacent sequences. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, etc. (see Bittner et al., 1987, *Methods in Enzymol.* 153:51-544).

[0212] In addition, a host cell strain may be chosen which modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (e.g., glycosylation) and processing (e.g., cleavage) of protein products may be important for the function of the protein. For example, in certain embodiments, the polypeptides of a heterodimeric trivalent/tetravalent multispecific antibody of the present disclosure may be expressed as a single gene product (e.g., as a single polypeptide chain, i.e., as a polyprotein precursor), requiring proteolytic cleavage by native or recombinant cellular mechanisms to form the separate polypeptides of the heterodimeric trivalent/tetravalent multispecific antibodies of the present disclosure. The present disclosure thus encom-

passes engineering a nucleic acid sequence to encode a polyprotein precursor molecule comprising the polypeptides of the heterodimeric trivalent/tetravalent multispecific antibodies of the present disclosure, which includes coding sequences capable of directing post translational cleavage of said polyprotein precursor. Post-translational cleavage of the polyprotein precursor results in the polypeptides of the heterodimeric trivalent/tetravalent multispecific antibodies of the present disclosure.

[0213] The post translational cleavage of the precursor molecule comprising the polypeptides of a heterodimeric trivalent/tetravalent multispecific antibody of the present disclosure may occur in vivo (i.e., within the host cell by native or recombinant cell systems/mechanisms, e.g. furin cleavage at an appropriate site) or may occur in vitro (e.g., incubation of said polypeptide chain in a composition comprising proteases or peptidases of known activity and/or in a composition comprising conditions or reagents known to foster the desired proteolytic action). Purification and modification of recombinant proteins are well known in the art such that the design of the polyprotein precursor could include a number of embodiments readily appreciated by a skilled artisan. Any known proteases or peptidases known in the art can be used for the described modification of the precursor molecule, e.g., thrombin (which recognizes the amino acid sequence LVPRˆGS (SEQ ID NO: 2500)), or factor Xa (which recognizes the amino acid sequence I(E/D)GRˆ (SEQ ID NO: 2501) (Nagani et al., 1985, *PNAS USA* 82:7252-7255, and reviewed in Jenny et al., 2003, *Protein Expr. Purif.* 31:1-11, each of which is incorporated by reference herein in its entirety)), enterokinase (which recognizes the amino acid sequence DDDDKˆ (SEQ ID NO: 2502) (Collins-Racie et al., 1995, *Biotechnol.* 13:982-987 hereby incorporated by reference herein in its entirety)), furin (which recognizes the amino acid sequence RXXRˆ, with a preference for RX(K/R)Rˆ (SEQ ID NO: 2503 and SEQ ID NO: 2504, respectively) (additional R at P6 position appears to enhance cleavage)), and AcTEV (which recognizes the amino acid sequence ENLYFQˆG (SEQ ID NO: 2505) (Parks et al., 1994, *Anal. Biochem.* 216:413 hereby incorporated by reference herein in its entirety)) and the Foot and Mouth Disease Virus Protease C3.

[0214] Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product may be used. Such mammalian host cells include but are not limited to CHO, VERY, BHK, Hela, COS, MDCK, 293, 293T, 3T3, WI38, BT483, Hs578T, HTB2, BT20 and T47D, CRL7030 and Hs578Bst.

[0215] For long-term, high-yield production of recombinant proteins, stable expression is desirable. For example, cell lines which stably express an antibody of the present disclosure may be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (e.g., promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer cell lines which express the antibodies of the present disclosure. Such engineered cell lines may be particularly useful in screening and evaluation of compounds that interact directly or indirectly with the heterodimeric trivalent/tetravalent multi specific antibodies of the present disclosure.

[0216] A number of selection systems may be used, including but not limited to the herpes simplex virus thymidine kinase (Wigler et al., 1977, *Cell* 11: 223), hypoxanthine-guanine phosphoribosyltransferase (Szybalska & Szybalski, 1992, *Proc. Natl. Acad. Sci. USA* 48: 202), and adenine phosphoribosyltransferase (Lowy et al., 1980, *Cell* 22: 817) genes can be employed in tk-, hgprt- or aprt-cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: dhfr, which confers resistance to methotrexate (Wigler et al., 1980, *Proc. Natl. Acad. Sci. USA* 77:357; O'Hare et al., 1981, *Proc. Natl. Acad. Sci. USA* 78: 1527); gpt, which confers resistance to mycophenolic acid (Mulligan & Berg, 1981, *Proc. Natl. Acad. Sci. USA* 78: 2072); neo, which confers resistance to the aminoglycoside G-418 *Clinical Pharmacy* 12: 488-505; Wu and Wu, 1991, 3:87-95; Tolstoshev, 1993, *Ann. Rev. Pharmacol. Toxicol.* 32:573-596; Mulligan, 1993, *Science* 260:926-932; and Morgan and Anderson, 1993, *Ann. Rev. Biochem.* 62:191-217; May, 1993, TIB TECH 11(5):155-215). Methods commonly known in the art of recombinant DNA technology which can be used are described in Ausubel et al. (eds.), 1993, *Current Protocols in Molecular Biology*, John Wiley & Sons, NY; Kriegler, 1990, *Gene Transfer and Expression*, A Laboratory Manual, Stockton Press, NY; and in Chapters 12 and 13, Dracopoli et al. (eds), 1994, *Current Protocols in Human Genetics*, John Wiley & Sons, NY.; Colberre-Garapin et al., 1981, *J. Mol. Biol.* 150:1; and hygro, which confers resistance to hygromycin (Santerre et al., 1984, *Gene* 30:147).

[0217] The expression levels of a heterodimeric trivalent/tetravalent multispecific antibody of the present disclosure can be increased by vector amplification (for a review, see Bebbington and Hentschel, *The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells in DNA cloning*, Vol. 3 (Academic Press, New York, 1987). When a marker in the vector system expressing an antibody is amplifiable, increase in the level of inhibitor present in culture of host cell will increase the number of copies of the selection marker gene. Since the amplified region is associated with the nucleotide sequence of a polypeptide of the heterodimeric trivalent/tetravalent multispecific antibody molecule, production of the polypeptide will also increase (Crouse et al., 1983, *Mol. Cell. Biol.* 3:257).

[0218] The host cell may be co-transfected with a plurality of expression vectors of the present disclosure, wherein each expression vector encodes at least one and no more than three of the first, second, third, or fourth polypeptide chains of the heterodimeric trivalent/tetravalent multispecific antibody. Alternatively, a single vector may be used which encodes the first, second, third, and fourth polypeptide chains of the heterodimeric trivalent/tetravalent multispe-

cific antibody. The coding sequences for the polypeptides of the heterodimeric trivalent/tetravalent multispecific antibodies of the present disclosure may comprise cDNA or genomic DNA.

[0219] Once a molecule of the present disclosure (i.e., heterodimeric trivalent/tetravalent multispecific antibodies) has been recombinantly expressed, it may be purified by any method known in the art for purification of polypeptides, polyproteins or heterodimeric trivalent/tetravalent multispecific antibodies (e.g., analogous to antibody purification schemes based on antigen selectivity) for example, by chromatography (e.g., ion exchange, affinity, particularly by affinity for the specific antigen (optionally after Protein A selection where the heterodimeric trivalent/tetravalent multispecific antibodies molecule comprises an Fc domain (or portion thereof)), and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of polypeptides, polyproteins or heterodimeric trivalent/tetravalent multispecific antibodies.

[0220] Labeled Heterodimeric trivalent/tetravalent multispecific antibodies. In one embodiment, the heterodimeric trivalent/tetravalent multispecific antibody of the present technology is coupled with a label moiety, i.e., detectable group. The particular label or detectable group conjugated to the heterodimeric trivalent/tetravalent multispecific antibody is not a critical aspect of the technology, so long as it does not significantly interfere with the specific binding of the heterodimeric trivalent/tetravalent multispecific antibody of the present technology to its target antigens. The detectable group can be any material having a detectable physical or chemical property. Such detectable labels have been well-developed in the field of immunoassays and imaging. In general, almost any label useful in such methods can be applied to the present technology. Thus, a label is any composition detectable by spectroscopic, photochemical, biochemical, immunochemical, electrical, optical or chemical means. Labels useful in the practice of the present technology include magnetic beads (e.g., Dynabeads™), fluorescent dyes (e.g., fluorescein isothiocyanate, Texas red, rhodamine, and the like), radiolabels (e.g., ^{3}H, ^{14}C, ^{35}S ^{125}I, ^{121}I, ^{131}I, ^{112}In, ^{99}mTc), other imaging agents such as microbubbles (for ultrasound imaging), ^{18}F, ^{11C}, ^{15}O, (for Positron emission tomography), ^{99m}Tc, ^{111}In (for Single photon emission tomography), enzymes (e.g., horse radish peroxidase, alkaline phosphatase and others commonly used in an ELISA), and calorimetric labels such as colloidal gold or colored glass or plastic (e.g., polystyrene, polypropylene, latex, and the like) beads. Patents that describe the use of such labels include U.S. Pat. Nos. 3,817,837; 3,850,752; 3,939,350; 3,996,345; 4,277,437; 4,275,149; and 4,366,241, each incorporated herein by reference in their entirety and for all purposes. See also Handbook of Fluorescent Probes and Research Chemicals (6^{th} Ed., Molecular Probes, Inc., Eugene Oreg.).

[0221] The label can be coupled directly or indirectly to the desired component of an assay according to methods well known in the art. As indicated above, a wide variety of labels can be used, with the choice of label depending on factors such as required sensitivity, ease of conjugation with the compound, stability requirements, available instrumentation, and disposal provisions.

[0222] Non-radioactive labels are often attached by indirect means. Generally, a ligand molecule (e.g., biotin) is covalently bound to the molecule. The ligand then binds to an anti-ligand (e.g., streptavidin) molecule which is either inherently detectable or covalently bound to a signal system, such as a detectable enzyme, a fluorescent compound, or a chemiluminescent compound. A number of ligands and anti-ligands can be used. Where a ligand has a natural anti-ligand, e.g., biotin, thyroxine, and cortisol, it can be used in conjunction with the labeled, naturally-occurring anti-ligands. Alternatively, any haptenic or antigenic compound can be used in combination with an antibody, e.g., a heterodimeric trivalent/tetravalent multispecific antibody.

[0223] The molecules can also be conjugated directly to signal generating compounds, e.g., by conjugation with an enzyme or fluorophore. Enzymes of interest as labels will primarily be hydrolases, particularly phosphatases, esterases and glycosidases, or oxidoreductases, particularly peroxidases. Fluorescent compounds useful as labeling moieties, include, but are not limited to, e.g., fluorescein and its derivatives, rhodamine and its derivatives, dansyl, umbelliferone, and the like. Chemiluminescent compounds useful as labeling moieties, include, but are not limited to, e.g., luciferin, and 2,3-dihydrophthalazinediones, e.g., luminol. For a review of various labeling or signal-producing systems which can be used, see U.S. Pat. No. 4,391,904.

[0224] Means of detecting labels are well known to those of skill in the art. Thus, for example, where the label is a radioactive label, means for detection include a scintillation counter or photographic film as in autoradiography. Where the label is a fluorescent label, it can be detected by exciting the fluorochrome with the appropriate wavelength of light and detecting the resulting fluorescence. The fluorescence can be detected visually, by means of photographic film, by the use of electronic detectors such as charge coupled devices (CCDs) or photomultipliers and the like. Similarly, enzymatic labels can be detected by providing the appropriate substrates for the enzyme and detecting the resulting reaction product. Finally simple colorimetric labels can be detected simply by observing the color associated with the label. Thus, in various dipstick assays, conjugated gold often appears pink, while various conjugated beads appear the color of the bead.

[0225] Some assay formats do not require the use of labeled components. For instance, agglutination assays can be used to detect the presence of the target antibodies, e.g., the heterodimeric trivalent/tetravalent multispecific antibodies. In this case, antigen-coated particles are agglutinated by samples comprising the target antibodies. In this format, none of the components need be labeled and the presence of the target antibody is detected by simple visual inspection.

[0226] Fusion Proteins. In one embodiment, the heterodimeric trivalent/tetravalent multispecific antibody of the present technology is a fusion protein. In some embodiments, the heterodimeric trivalent/tetravalent multispecific antibodies of the present technology, when fused to a second protein, can be used as an antigenic tag. Examples of domains that can be fused to polypeptides include not only heterologous signal sequences, but also other heterologous functional regions. The fusion does not necessarily need to be direct, but can occur through linker sequences. Moreover, fusion proteins of the present technology can also be engineered to improve characteristics of the heterodimeric trivalent/tetravalent multispecific antibodies. For instance, a region of additional amino acids, particularly charged amino acids, can be added to the N-terminus of the heterodimeric

trivalent/tetravalent multispecific antibody to improve stability and persistence during purification from the host cell or subsequent handling and storage. Also, peptide moieties can be added to a heterodimeric trivalent/tetravalent multispecific antibody to facilitate purification. Such regions can be removed prior to final preparation of the heterodimeric trivalent/tetravalent multispecific antibody. The addition of peptide moieties to facilitate handling of polypeptides may be accomplished using familiar and routine techniques in the art. The heterodimeric trivalent/tetravalent multispecific antibody of the present technology can be fused to marker sequences, such as a peptide which facilitates purification of the fused polypeptide. In select embodiments, the marker amino acid sequence is a hexa-histidine peptide (SEQ ID NO: 2510), such as the tag provided in a pQE vector (QIAGEN, Inc., Chatsworth, Calif.), among others, many of which are commercially available. As described in Gentz et al., *Proc. Natl. Acad. Sci. USA* 86: 821-824, 1989, for instance, hexa-histidine (SEQ ID NO: 2510) provides for convenient purification of the fusion protein. Another peptide tag useful for purification, the "HA" tag, corresponds to an epitope derived from the influenza hemagglutinin protein. Wilson et al., *Cell* 37: 767, 1984.

[0227] Thus, any of these above fusion proteins can be engineered using the polynucleotides or the polypeptides of the present technology. Also, in some embodiments, the fusion proteins described herein show an increased half-life in vivo.

[0228] Fusion proteins having disulfide-linked dimeric structures (due to the IgG) can be more efficient in binding and neutralizing other molecules compared to the monomeric secreted protein or protein fragment alone. Fountoulakis et al., *J. Biochem.* 270: 3958-3964, 1995.

[0229] Similarly, EP-A-O 464 533 (Canadian counterpart 2045869) discloses fusion proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or a fragment thereof. In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, e.g., improved pharmacokinetic properties. See EP-A 0232 262. Alternatively, deleting or modifying the Fc part after the fusion protein has been expressed, detected, and purified, may be desired. For example, the Fc portion can hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, e.g., human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. Bennett et al., *J. Molecular Recognition* 8: 52-58, 1995; Johanson et al., *J. Biol. Chem.,* 270: 9459-9471, 1995.

[0230] In some embodiments, the heterodimeric trivalent/tetravalent multispecific antibody of the present technology may be conjugated to a therapeutic agent or a payload. Examples of a payload include a toxin, a protein such as tumor necrosis factor, interferons including, but not limited to, α-interferon (IFN-α), β-interferon (IFN-β), nerve growth factor (NGF), platelet derived growth factor (PDGF), tissue plasminogen activator (TPA), an apoptotic agent (e.g., TNF-α, TNF-β, AIM I as disclosed in PCT Publication No. WO 97/33899), AIM II (see, PCT Publication No. WO 97/34911), Fas ligand (Takahashi et al., *J. Immunol.,* 6:1567-1574, 1994), and VEGI (PCT Publication No. WO 99/23105), a thrombotic agent or an anti-angiogenic agent (e.g., angiostatin or endostatin), or a biological response modifier such as, for example, a lymphokine (e.g., interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), and granulocyte colony stimulating factor ("G-CSF"), macrophage colony stimulating factor, ("M-CSF"), or a growth factor (e.g., growth hormone ("GH"); proteases, or ribonucleases. Examples of therapeutic agents include paclitaxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Other examples of therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclothosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cisdichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC), and anti-mitotic agents (e.g., vincristine and vinblastine).

B. Identifying and Characterizing the Heterodimeric Trivalent/Tetravalent Multispecific Antibodies of the Present Technology

[0231] Methods for identifying and/or screening the heterodimeric trivalent/tetravalent multispecific antibodies of the present technology. Methods useful to identify and screen antibodies that possess the desired specificity to a target antigen include any immunologically-mediated techniques known within the art. Components of an immune response can be detected in vitro by various methods that are well known to those of ordinary skill in the art. For example, (1) cytotoxic T lymphocytes can be incubated with radioactively labeled target cells and the lysis of these target cells detected by the release of radioactivity; (2) helper T lymphocytes can be incubated with antigens and antigen presenting cells and the synthesis and secretion of cytokines measured by standard methods (Windhagen A et al., *Immunity,* 2: 373-80, 1995); (3) antigen presenting cells can be incubated with whole protein antigen and the presentation of that antigen on MHC detected by either T lymphocyte activation assays or biophysical methods (Harding et al., *Proc. Natl. Acad. Sci.,* 86: 4230-4, 1989); (4) mast cells can be incubated with reagents that cross-link their Fc-epsilon receptors and histamine release measured by enzyme immunoassay (Siraganian et al., *TIPS,* 4: 432-437, 1983); and (5) enzyme-linked immunosorbent assay (ELISA).

[0232] Similarly, products of an immune response in either a model organism (e.g., mouse) or a human subject can also be detected by various methods that are well known to those of ordinary skill in the art. For example, (1) the production of antibodies in response to vaccination can be readily detected by standard methods currently used in clinical laboratories, e.g., an ELISA; (2) the migration of immune cells to sites of inflammation can be detected by scratching the surface of skin and placing a sterile container to capture the migrating cells over scratch site (Peters et al., *Blood,* 72: 1310-5, 1988); (3) the proliferation of peripheral

blood mononuclear cells (PBMCs) in response to mitogens or mixed lymphocyte reaction can be measured using ^{3}H-thymidine; (4) the phagocytic capacity of granulocytes, macrophages, and other phagocytes in PBMCs can be measured by placing PBMCs in wells together with labeled particles (Peters et al., *Blood,* 72: 1310-5, 1988); and (5) the differentiation of immune system cells can be measured by labeling PBMCs with antibodies to CD molecules such as CD4 and CD8 and measuring the fraction of the PBMCs expressing these markers.

[0233] In one embodiment, heterodimeric trivalent/tetravalent multispecific antibodies of the present technology are selected using display of target antigen peptides on the surface of replicable genetic packages. See, e.g., U.S. Pat. Nos. 5,514,548; 5,837,500; 5,871,907; 5,885,793; 5,969,108; 6,225,447; 6,291,650; 6,492,160; EP 585 287; EP 605522; EP 616640; EP 1024191; EP 589 877; EP 774 511; EP 844 306. Methods useful for producing/selecting a filamentous bacteriophage particle containing a phagemid genome encoding for a binding molecule with a desired specificity has been described. See, e.g., EP 774 511; U.S. Pat. Nos. 5,871,907; 5,969,108; 6,225,447; 6,291,650; 6,492,160.

[0234] In some embodiments, heterodimeric trivalent/tetravalent multispecific antibodies of the present technology are selected using display of target antigen peptides on the surface of a yeast host cell. Methods useful for the isolation of scFv polypeptides by yeast surface display have been described by Kieke et al., *Protein Eng.* 1997 November; 10(11): 1303-10.

[0235] In some embodiments, heterodimeric trivalent/tetravalent multispecific antibodies of the present technology are selected using ribosome display. Methods useful for identifying ligands in peptide libraries using ribosome display have been described by Mattheakis et al., *Proc. Natl. Acad. Sci. USA* 91: 9022-26, 1994; and Hanes et al., *Proc. Natl. Acad. Sci. USA* 94: 4937-42, 1997.

[0236] In certain embodiments, heterodimeric trivalent/tetravalent multispecific antibodies of the present technology are selected using tRNA display of target antigen peptides. Methods useful for in vitro selection of ligands using tRNA display have been described by Merryman et al., *Chem. Biol.,* 9: 741-46, 2002.

[0237] In one embodiment, heterodimeric trivalent/tetravalent multispecific antibodies of the present technology are selected using RNA display. Methods useful for selecting peptides and proteins using RNA display libraries have been described by Roberts et al. *Proc. Natl. Acad. Sci. USA,* 94: 12297-302, 1997; and Nemoto et al., *FEBS Lett.,* 414: 405-8, 1997. Methods useful for selecting peptides and proteins using unnatural RNA display libraries have been described by Frankel et al., *Curr. Opin. Struct. Biol.,* 13: 506-12, 2003.

[0238] In some embodiments, heterodimeric trivalent/tetravalent multispecific antibodies of the present technology are expressed in the periplasm of gram negative bacteria and mixed with labeled target antigen. See WO 02/34886. In clones expressing recombinant polypeptides with affinity for a target antigen, the concentration of the labeled target antigen bound to the heterodimeric trivalent/tetravalent multispecific antibodies is increased and allows the cells to be isolated from the rest of the library as described in Harvey et al., *Proc. Natl. Acad. Sci.* 22: 9193-98 2004 and U.S. Pat. Publication No. 2004/0058403.

[0239] After selection of the desired heterodimeric trivalent/tetravalent multispecific antibodies, it is contemplated that said antibodies can be produced in large volume by any technique known to those skilled in the art, e.g., prokaryotic or eukaryotic cell expression and the like. For example, the heterodimeric trivalent/tetravalent multispecific antibodies can be produced by using conventional techniques to construct an expression vector that encodes an antibody heavy chain and/or light chain in which the CDRs and, if necessary, a minimal portion of the variable region framework, that are required to retain original species antibody binding specificity (as engineered according to the techniques described herein) are derived from the originating species antibody and the remainder of the antibody is derived from a target species immunoglobulin which can be manipulated as described herein, thereby producing a vector for the expression of a hybrid antibody heavy chain.

[0240] Measurement of Antigen Binding. In some embodiments, an antigen binding assay refers to an assay format wherein a target antigen and a heterodimeric trivalent/tetravalent multispecific antibody are mixed under conditions suitable for binding between the target antigen and the heterodimeric trivalent/tetravalent multispecific antibody and assessing the amount of binding between the target antigen and the heterodimeric trivalent/tetravalent multispecific antibody. The amount of binding is compared with a suitable control, which can be the amount of binding in the absence of the target antigen, the amount of the binding in the presence of a non-specific immunoglobulin composition, or both. The amount of binding can be assessed by any suitable method. Binding assay methods include, e.g., ELISA, radioimmunoassays, scintillation proximity assays, fluorescence energy transfer assays, liquid chromatography, membrane filtration assays, and the like. Biophysical assays for the direct measurement of target antigen binding to a heterodimeric trivalent/tetravalent multispecific antibody are, e.g., nuclear magnetic resonance, fluorescence, fluorescence polarization, surface plasmon resonance (BIACORE chips) and the like. Specific binding is determined by standard assays known in the art, e.g., radioligand binding assays, ELISA, FRET, immunoprecipitation, SPR, NMR (2D-NMR), mass spectroscopy and the like. If the specific binding of a candidate heterodimeric trivalent/tetravalent multispecific antibody is at least 1 percent greater than the binding observed in the absence of the candidate heterodimeric trivalent/tetravalent multispecific antibody, the candidate heterodimeric trivalent/tetravalent multi specific antibody is useful as a heterodimeric trivalent/tetravalent multispecific antibody of the present technology.

[0241] Measurement of Target Antigen Neutralization. As used here, "target antigen neutralization" refers to reduction of the activity and/or expression of a target antigen through the binding of a heterodimeric trivalent/tetravalent multispecific antibody disclosed herein. The capacity of heterodimeric trivalent/tetravalent multispecific antibodies of the present technology to neutralize activity/expression of a target antigen may be assessed in vitro or in vivo using methods known in the art.

Uses of the Heterodimeric Trivalent/Tetravalent Multispecific Antibodies of the Present Technology

[0242] General. The heterodimeric trivalent/tetravalent multispecific antibodies of the present technology are useful in methods known in the art relating to the localization

and/or quantitation of a target antigen (e.g., for use in measuring levels of the target antigen within appropriate physiological samples, for use in diagnostic methods, for use in imaging the target antigen, and the like). Antibodies of the present technology are useful to isolate a target antigen by standard techniques, such as affinity chromatography or immunoprecipitation. A heterodimeric trivalent/tetravalent multispecific antibody of the present technology can facilitate the purification of natural immunoreactive target antigens from biological samples, e.g., mammalian sera or cells as well as recombinantly-produced immunoreactive target antigens expressed in a host system. Moreover, heterodimeric trivalent/tetravalent multispecific antibodies can be used to detect an immunoreactive target antigen (e.g., in plasma, a cellular lysate or cell supernatant) in order to evaluate the abundance and pattern of expression of the immunoreactive molecule. The heterodimeric trivalent/tetravalent multispecific antibodies of the present technology can be used diagnostically to monitor immunoreactive target antigen levels in tissue as part of a clinical testing procedure, e.g., to determine the efficacy of a given treatment regimen. As noted above, the detection can be facilitated by coupling (i.e., physically linking) the heterodimeric trivalent/tetravalent multispecific antibodies of the present technology to a detectable sub stance.

[0243] Detection of target antigen. An exemplary method for detecting the presence or absence of an immunoreactive target antigen in a biological sample involves obtaining a biological sample from a test subject and contacting the biological sample with a heterodimeric trivalent/tetravalent multispecific antibody of the present technology capable of detecting an immunoreactive target antigen such that the presence of an immunoreactive target antigen is detected in the biological sample. Detection may be accomplished by means of a detectable label attached to the antibody.

[0244] The term "labeled" with regard to the heterodimeric trivalent/tetravalent multispecific antibody is intended to encompass direct labeling of the antibody by coupling (i.e., physically linking) a detectable substance to the antibody, as well as indirect labeling of the antibody by reactivity with another compound that is directly labeled, such as a secondary antibody. Examples of indirect labeling include detection of a primary antibody using a fluorescently-labeled secondary antibody and end-labeling of a DNA probe with biotin such that it can be detected with fluorescently-labeled streptavidin.

[0245] In some embodiments, the heterodimeric trivalent/tetravalent multispecific antibodies disclosed herein are conjugated to one or more detectable labels. For such uses, heterodimeric trivalent/tetravalent multispecific antibodies may be detectably labeled by covalent or non-covalent attachment of a chromogenic, enzymatic, radioisotopic, isotopic, fluorescent, toxic, chemiluminescent, nuclear magnetic resonance contrast agent or other label.

[0246] Examples of suitable chromogenic labels include diaminobenzidine and 4-hydroxyazo-benzene-2-carboxylic acid. Examples of suitable enzyme labels include malate dehydrogenase, staphylococcal nuclease, Δ-5-steroid isomerase, yeast-alcohol dehydrogenase, α-glycerol phosphate dehydrogenase, triose phosphate isomerase, peroxidase, alkaline phosphatase, asparaginase, glucose oxidase, β-galactosidase, ribonuclease, urease, catalase, glucose-6-phosphate dehydrogenase, glucoamylase, and acetylcholine esterase.

[0247] Examples of suitable radioisotopic labels include ^{3}H, ^{111}In, ^{125}I, ^{131}I, ^{32}P, ^{35}S, ^{14}C, ^{51}Cr, ^{57}To, ^{58}Co, ^{59}Fe, ^{75}Se, ^{152}Eu, ^{90}Y, ^{67}Cu, ^{217}Ci, ^{211}At, ^{212}Pb, ^{47}Sc, ^{109}Pd, etc. ^{111}In is an exemplary isotope where in vivo imaging is used since it avoids the problem of dehalogenation of the ^{125}I or ^{131}I-labeled heterodimeric trivalent/tetravalent multispecific antibodies by the liver. In addition, this isotope has a more favorable gamma emission energy for imaging (Perkins et al, *Eur. J. Nucl. Med.* 70:296-301 (1985); Carasquillo et al., *J. Nucl. Med.* 25:281-287 (1987)). For example, ^{111}In coupled to monoclonal antibodies with 1-(P-isothiocyanatobenzyl)-DPTA exhibits little uptake in non-tumorous tissues, particularly the liver, and enhances specificity of tumor localization (Esteban et al., *J. Nucl. Med.* 28:861-870 (1987)). Examples of suitable non-radioactive isotopic labels include ^{157}Gd, ^{55}Mn, ^{162}Dy, ^{52}Tr, and ^{56}Fe.

[0248] Examples of suitable fluorescent labels include an ^{152}Eu label, a fluorescein label, an isothiocyanate label, a rhodamine label, a phycoerythrin label, a phycocyanin label, an allophycocyanin label, a Green Fluorescent Protein (GFP) label, an o-phthaldehyde label, and a fluorescamine label. Examples of suitable toxin labels include diphtheria toxin, ricin, and cholera toxin.

[0249] Examples of chemiluminescent labels include a luminol label, an isoluminol label, an aromatic acridinium ester label, an imidazole label, an acridinium salt label, an oxalate ester label, a luciferin label, a luciferase label, and an aequorin label. Examples of nuclear magnetic resonance contrasting agents include heavy metal nuclei such as Gd, Mn, and iron.

[0250] The detection method of the present technology can be used to detect an immunoreactive target antigen in a biological sample in vitro as well as in vivo. In vitro techniques for detection of an immunoreactive target antigen include enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations, radioimmunoassay, and immunofluorescence. Furthermore, in vivo techniques for detection of an immunoreactive target antigen include introducing into a subject a labeled heterodimeric trivalent/tetravalent multispecific antibody. For example, the heterodimeric trivalent/tetravalent multispecific antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques. In one embodiment, the biological sample contains target antigen molecules from the test subject.

[0251] Immunoassay and Imaging. A heterodimeric trivalent/tetravalent multispecific antibody of the present technology can be used to assay immunoreactive target antigen levels in a biological sample (e.g., human plasma) using antibody-based techniques. For example, protein expression in tissues can be studied with classical immunohistological methods. Jalkanen, M. et al., *J. Cell. Biol.* 101: 976-985, 1985; Jalkanen, M. et al., *J. Cell. Biol.* 105: 3087-3096, 1987. Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase, and radioisotopes or other radioactive agent, such as iodine (^{125}I, ^{121}I, ^{131}I), and carbon (^{14}C), sulfur (^{35}S), tritium (^{3}H), indium (^{112}In), and technetium (^{99}mTc), and fluorescent labels, such as fluorescein, rhodamine, and green fluorescent protein (GFP), as well as biotin.

[0252] In addition to assaying immunoreactive target antigen levels in a biological sample, heterodimeric trivalent/tetravalent multispecific antibodies of the present technology may be used for in vivo imaging of the target antigen. Antibodies useful for this method include those detectable by X-radiography, NMR or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which can be incorporated into the heterodimeric trivalent/tetravalent multispecific antibodies by labeling of nutrients for the relevant scFv clone.

[0253] A heterodimeric trivalent/tetravalent multispecific antibody which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (e.g., ^{131}I, ^{112}In, ^{99}mTc), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (e.g., parenterally, subcutaneously, or intraperitoneally) into the subject. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of ^{99}mTc. The labeled heterodimeric trivalent/tetravalent multispecific antibody will then accumulate at the location of cells which contain the specific target antigen. For example, labeled heterodimeric trivalent/tetravalent multispecific antibodies of the present technology will accumulate within the subject in cells and tissues in which the target antigen has localized.

[0254] Thus, the present technology provides a diagnostic method of a medical condition, which involves: (a) assaying the expression of immunoreactive target antigen by measuring binding of a heterodimeric trivalent/tetravalent multispecific antibody of the present technology in cells or body fluid of an individual; (b) comparing the amount of immunoreactive target antigen present in the sample with a standard reference, wherein an increase or decrease in immunoreactive target antigen levels compared to the standard is indicative of a medical condition.

[0255] Affinity Purification. The heterodimeric trivalent/tetravalent multispecific antibodies of the present technology may be used to purify immunoreactive target antigen from a sample. In some embodiments, the antibodies are immobilized on a solid support. Examples of such solid supports include plastics such as polycarbonate, complex carbohydrates such as agarose and sepharose, acrylic resins and such as polyacrylamide and latex beads. Techniques for coupling antibodies to such solid supports are well known in the art (Weir et al., "Handbook of Experimental Immunology" 4th Ed., Blackwell Scientific Publications, Oxford, England, Chapter 10 (1986); Jacoby et al., *Meth. Enzym.* 34 Academic Press, N.Y. (1974)).

[0256] The simplest method to bind the antigen to the antibody-support matrix is to collect the beads in a column and pass the antigen solution down the column. The efficiency of this method depends on the contact time between the immobilized antibody and the antigen, which can be extended by using low flow rates. The immobilized antibody captures the antigen as it flows past. Alternatively, an antigen can be contacted with the antibody-support matrix by mixing the antigen solution with the support (e.g., beads) and rotating or rocking the slurry, allowing maximum contact between the antigen and the immobilized antibody. After the binding reaction has been completed, the slurry is passed into a column for collection of the beads. The beads are washed using a suitable washing buffer and then the pure or substantially pure antigen is eluted.

[0257] An antibody or target antigen of interest can be conjugated to a solid support, such as a bead. In addition, a first solid support such as a bead can also be conjugated, if desired, to a second solid support, which can be a second bead or other support, by any suitable means, including those disclosed herein for conjugation of a molecule to a support. Accordingly, any of the conjugation methods and means disclosed herein with reference to conjugation of a molecule to a solid support can also be applied for conjugation of a first support to a second support, where the first and second solid support can be the same or different.

[0258] Appropriate linkers, which can be cross-linking agents, for use for conjugating a molecule to a solid support include a variety of agents that can react with a functional group present on a surface of the support, or with the molecule, or both. Reagents useful as cross-linking agents include homo-bi-functional and, in particular, hetero-bi-functional reagents. Useful bi-functional cross-linking agents include, but are not limited to, N-SIAB, dimaleimide, DTNB, N-SATA, N-SPDP, SMCC and 6-HYNIC. In one exemplary embodiment, a cross-linking agent can be selected to provide a selectively cleavable bond between a target polypeptide and the solid support. For example, a photolabile cross-linker, such as 3-amino-(2-nitrophenyl) propionic acid can be employed as a means for cleaving a target polypeptide from a solid support. (Brown et al., *Mol. Divers*, pp, 4-12 (1995); Rothschild et al., *Nucl. Acids Res.*, 24:351-66 (1996); and U.S. Pat. No. 5,643,722). Other cross-linking reagents are well-known in the art. (See, e.g., Wong (1991), supra; and Hermanson (1996), supra).

[0259] An antibody or target polypeptide can be immobilized on a solid support, such as a bead, through a covalent amide bond formed between a carboxyl group functionalized bead and the amino terminus of the target polypeptide or, conversely, through a covalent amide bond formed between an amino group functionalized bead and the carboxyl terminus of the target polypeptide. In addition, a bi-functional trityl linker can be attached to the support, e.g., to the 4-nitrophenyl active ester on a resin, such as a Wang resin, through an amino group or a carboxyl group on the resin via an amino resin. Using a bi-functional trityl approach, the solid support can require treatment with a volatile acid, such as formic acid or trifluoroacetic acid to ensure that the target polypeptide is cleaved and can be removed. In such a case, the target polypeptide can be deposited as a beadless patch at the bottom of a well of a solid support or on the flat surface of a solid support. After addition of a matrix solution, the target polypeptide can be desorbed into a MS.

[0260] Hydrophobic trityl linkers can also be exploited as acid-labile linkers by using a volatile acid or an appropriate matrix solution, e.g., a matrix solution containing 3-HPA, to cleave an amino linked trityl group from the target polypeptide. Acid lability can also be changed. For example, trityl, monomethoxytrityl, dimethoxytrityl or trimethoxytrityl can be changed to the appropriate p-substituted, or more acid-labile tritylamine derivatives, of the target polypeptide, i.e., trityl ether and tritylamine bonds can be made to the target polypeptide. Accordingly, a target polypeptide can be

removed from a hydrophobic linker, e.g., by disrupting the hydrophobic attraction or by cleaving tritylether or tritylamine bonds under acidic conditions, including, if desired, under typical MS conditions, where a matrix, such as 3-HPA acts as an acid.

[0261] Orthogonally cleavable linkers can also be useful for binding a first solid support, e.g., a bead to a second solid support, or for binding a molecule of interest to a solid support. Using such linkers, a first solid support, e.g., a bead, can be selectively cleaved from a second solid support, without cleaving the target antigen from the support; the target antigen then can be cleaved from the bead at a later time. For example, a disulfide linker, which can be cleaved using a reducing agent, such as DTT, can be employed to bind a bead to a second solid support, and an acid cleavable bi-functional trityl group could be used to immobilize a target antigen to the support. As desired, the linkage of the target antigen to the solid support can be cleaved first, e.g., leaving the linkage between the first and second support intact. Trityl linkers can provide a covalent or hydrophobic conjugation and, regardless of the nature of the conjugation, the trityl group is readily cleaved in acidic conditions.

[0262] For example, a bead can be bound to a second support through a linking group which can be selected to have a length and a chemical nature such that high density binding of the beads to the solid support, or high density binding of the target antigens to the beads, is promoted. Such a linking group can have, e.g., "tree-like" structure, thereby providing a multiplicity of functional groups per attachment site on a solid support. Examples of such linking group; include polylysine, polyglutamic acid, penta-erythrole and tris-hydroxy-aminomethane.

[0263] Noncovalent Binding Association. An antibody or target antigen can be conjugated to a solid support, or a first solid support can also be conjugated to a second solid support, through a noncovalent interaction. For example, a magnetic bead made of a ferromagnetic material, which is capable of being magnetized, can be attracted to a magnetic solid support, and can be released from the support by removal of the magnetic field. Alternatively, the solid support can be provided with an ionic or hydrophobic moiety, which can allow the interaction of an ionic or hydrophobic moiety, respectively, with a target antigen, e.g., a polypeptide containing an attached trityl group or with a second solid support having hydrophobic character.

[0264] A solid support can also be provided with a member of a specific binding pair and, therefore, can be conjugated to a target antigen or a second solid support containing a complementary binding moiety. For example, a bead coated with avidin or with streptavidin can be bound to a target antigen (e.g., a polypeptide) having a biotin moiety incorporated therein, or to a second solid support coated with biotin or derivative of biotin, such as iminobiotin.

[0265] It should be recognized that any of the binding members disclosed herein or otherwise known in the art can be reversed. Thus, biotin, e.g., can be incorporated into either a target antigen or a solid support and, conversely, avidin or other biotin binding moiety would be incorporated into the support or the target antigen, respectively. Other specific binding pairs contemplated for use herein include, but are not limited to, hormones and their receptors, enzyme, and their substrates, a nucleotide sequence and its complementary sequence, an antibody and the antigen to which it interacts specifically, and other such pairs known to those skilled in the art.

A. Diagnostic Uses

[0266] General. The heterodimeric trivalent/tetravalent multispecific antibodies of the present technology are useful in diagnostic methods. As such, the present technology provides methods using the antibodies in the diagnosis of activity of a molecule of interest in a subject. Heterodimeric trivalent/tetravalent multispecific antibodies of the present technology may be selected such that they have any level of epitope binding specificity and binding affinity to a target antigen. In general, the higher the binding affinity of an antibody, the more stringent wash conditions can be performed in an immunoassay to remove nonspecifically bound material without removing the molecule of interest. Accordingly, heterodimeric trivalent/tetravalent multispecific antibodies of the present technology useful in diagnostic assays usually have binding affinities of about $10^8 M^{-1}$, $10^9 M^{-1}$, $10^{10} M^{-1}$, $10^{11} M^{-1}$ or $10^{12} M^{-1}$. Further, it is desirable that heterodimeric trivalent/tetravalent multispecific antibodies used as diagnostic reagents have a sufficient kinetic on-rate to reach equilibrium under standard conditions in at least 12 h, at least five (5) h, or at least one (1) hour.

[0267] Heterodimeric trivalent/tetravalent multispecific antibodies can be used to detect an immunoreactive target antigen in a variety of standard assay formats. Such formats include immunoprecipitation, Western blotting, ELISA, radioimmunoassay, and immunometric assays. See Harlow & Lane, *Antibodies, A Laboratory Manual* (Cold Spring Harbor Publications, New York, 1988); U.S. Pat. Nos. 3,791,932; 3,839,153; 3,850,752; 3,879,262; 4,034,074, 3,791,932; 3,817,837; 3,839,153; 3,850,752; 3,850,578; 3,853,987; 3,867,517; 3,879,262; 3,901,654; 3,935,074; 3,984,533; 3,996,345; 4,034,074; and 4,098,876. Biological samples can be obtained from any tissue or body fluid of a subject. In certain embodiments, the subject is at an early stage of cancer. In one embodiment, the early stage of cancer is determined by the level or expression pattern of a target antigen in a sample obtained from the subject. In certain embodiments, the sample is selected from the group consisting of urine, blood, serum, plasma, saliva, amniotic fluid, cerebrospinal fluid (CSF), and biopsied body tissue.

[0268] Immunometric or sandwich assays are one format for the diagnostic methods of the present technology. See U.S. Pat. Nos. 4,376,110, 4,486,530, 5,914,241, and 5,965, 375. Such assays use one antibody, e.g., a heterodimeric trivalent/tetravalent multispecific antibody or a population of heterodimeric trivalent/tetravalent multispecific antibodies immobilized to a solid phase, and another heterodimeric trivalent/tetravalent multispecific antibody or a population of heterodimeric trivalent/tetravalent multispecific antibodies in solution. Typically, the solution heterodimeric trivalent/tetravalent multispecific antibody or population of heterodimeric trivalent/tetravalent multispecific antibodies is labeled. If an antibody population is used, the population can contain antibodies binding to different epitope specificities within the target antigen. Accordingly, the same population can be used for both solid phase and solution antibody. If heterodimeric trivalent/tetravalent multispecific monoclonal antibodies are used, first and second monoclonal heterodimeric trivalent/tetravalent multispecific antibodies having different binding specificities are used for the solid and

solution phase. Solid phase (also referred to as "capture") and solution (also referred to as "detection") antibodies can be contacted with target antigen in either order or simultaneously. If the solid phase antibody is contacted first, the assay is referred to as being a forward assay. Conversely, if the solution antibody is contacted first, the assay is referred to as being a reverse assay. If the target is contacted with both antibodies simultaneously, the assay is referred to as a simultaneous assay. After contacting the target antigen with the heterodimeric trivalent/tetravalent multispecific antibody, a sample is incubated for a period that usually varies from about 10 min to about 24 hr and is usually about 1 hr. A wash step is then performed to remove components of the sample not specifically bound to the heterodimeric trivalent/tetravalent multispecific antibody being used as a diagnostic reagent. When solid phase and solution antibodies are bound in separate steps, a wash can be performed after either or both binding steps. After washing, binding is quantified, typically by detecting a label linked to the solid phase through binding of labeled solution antibody. Usually for a given pair of antibodies or populations of antibodies and given reaction conditions, a calibration curve is prepared from samples containing known concentrations of target antigen. Concentrations of the immunoreactive target antigen in samples being tested are then read by interpolation from the calibration curve (i.e., standard curve). Analyte can be measured either from the amount of labeled solution antibody bound at equilibrium or by kinetic measurements of bound labeled solution antibody at a series of time points before equilibrium is reached. The slope of such a curve is a measure of the concentration of the target antigen in a sample.

[0269] Suitable supports for use in the above methods include, e.g., nitrocellulose membranes, nylon membranes, and derivatized nylon membranes, and also particles, such as agarose, a dextran-based gel, dipsticks, particulates, microspheres, magnetic particles, test tubes, microtiter wells, SEPHADEX™ (Amersham Pharmacia Biotech, Piscataway N.J.), and the like. Immobilization can be by absorption or by covalent attachment. Optionally, heterodimeric trivalent/tetravalent multispecific antibodies can be joined to a linker molecule, such as biotin for attachment to a surface bound linker, such as avidin.

[0270] In some embodiments, the present disclosure provides a heterodimeric trivalent/tetravalent multispecific antibody of the present technology conjugated to a diagnostic agent. The diagnostic agent may comprise a radioactive or non-radioactive label, a contrast agent (such as for magnetic resonance imaging, computed tomography or ultrasound), and the radioactive label can be a gamma-, beta-, alpha-, Auger electron-, or positron-emitting isotope. A diagnostic agent is a molecule which is administered conjugated to an antibody moiety, i.e., antibody or antibody fragment, or subfragment, and is useful in diagnosing or detecting a disease by locating the cells containing the antigen. Radioactive levels emitted by the antibody may be detected using positron emission tomography or single photon emission computed tomography.

[0271] Useful diagnostic agents include, but are not limited to, radioisotopes, dyes (such as with the biotin-streptavidin complex), contrast agents, fluorescent compounds or molecules and enhancing agents (e.g., paramagnetic ions) for magnetic resonance imaging (MRI). U.S. Pat. No. 6,331,175 describes MRI technique and the preparation of antibodies conjugated to a MRI enhancing agent and is incorporated in its entirety by reference. In some embodiments, the diagnostic agents are selected from the group consisting of radioisotopes, enhancing agents for use in magnetic resonance imaging, and fluorescent compounds. In order to load an antibody component with radioactive metals or paramagnetic ions, it may be necessary to react it with a reagent having a long tail to which are attached a multiplicity of chelating groups for binding the ions. Such a tail can be a polymer such as a polylysine, polysaccharide, or other derivatized or derivatizable chain having pendant groups to which can be bound chelating groups such as, e.g., ethylenediaminetetraacetic acid (EDTA), diethylenetriaminepentaacetic acid (DTPA), porphyrins, polyamines, crown ethers, bis-thiosemicarbazones, polyoximes, and like groups known to be useful for this purpose. Chelates may be coupled to the antibodies of the present technology using standard chemistries. The chelate is normally linked to the antibody by a group which enables formation of a bond to the molecule with minimal loss of immunoreactivity and minimal aggregation and/or internal cross-linking. Other methods and reagents for conjugating chelates to antibodies are disclosed in U.S. Pat. No. 4,824,659. Particularly useful metal-chelate combinations include 2-benzyl-DTPA and its monomethyl and cyclohexyl analogs, used with diagnostic isotopes for radio-imaging. The same chelates, when complexed with non-radioactive metals, such as manganese, iron and gadolinium are useful for MM, when used along with the heterodimeric trivalent/tetravalent multispecific antibodies of the present technology.

B. Therapeutic Uses

[0272] The immunoglobulin-related compositions (e.g., heterodimeric trivalent/tetravalent multispecific antibodies) of the present technology are useful for the treatment of a disease or condition. Exemplary diseases or conditions include, but are not limited to cardiovascular disease, diabetes, autoimmune disease, dementia, Parkinson's disease, cancer or Alzheimer's disease. Such treatment can be used in patients identified as having pathological levels of a molecule of interest (e.g., those diagnosed by the methods described herein) or in patients diagnosed with a disease known to be associated with such pathological levels. In one aspect, the present disclosure provides a method for treating cancer in a subject in need thereof, comprising administering to the subject an effective amount of a heterodimeric trivalent/tetravalent multispecific antibody of the present technology. Examples of cancers that can be treated by the antibodies of the present technology include, but are not limited to: lung cancer, colorectal cancer, skin cancer, breast cancer, ovarian cancer, leukemia, pancreatic cancer, and gastric cancer.

[0273] The compositions of the present technology may be employed in conjunction with other therapeutic agents useful in the treatment of cancer. For example, the antibodies of the present technology may be separately, sequentially or simultaneously administered with at least one additional therapeutic agent-selected from the group consisting of alkylating agents, platinum agents, taxanes, vinca agents, anti-estrogen drugs, aromatase inhibitors, ovarian suppression agents, VEGF/VEGFR inhibitors, EGF/EGFR inhibitors, PARP inhibitors, cytostatic alkaloids, cytotoxic antibiotics, antimetabolites, endocrine/hormonal agents, bisphosphonate therapy agents and targeted biological

therapy agents (e.g., therapeutic peptides described in U.S. Pat. No. 6,306,832, WO 2012007137, WO 2005000889, WO 2010096603 etc.). In some embodiments, the at least one additional therapeutic agent is a chemotherapeutic agent. Specific chemotherapeutic agents include, but are not limited to, cyclophosphamide, fluorouracil (or 5-fluorouracil or 5-FU), methotrexate, edatrexate (10-ethyl-10-deaza-aminopterin), thiotepa, carboplatin, cisplatin, taxanes, paclitaxel, protein-bound paclitaxel, docetaxel, vinorelbine, tamoxifen, raloxifene, toremifene, fulvestrant, gemcitabine, irinotecan, ixabepilone, temozolmide, topotecan, vincristine, vinblastine, eribulin, mutamycin, capecitabine, anastrozole, exemestane, letrozole, leuprolide, abarelix, buserlin, goserelin, megestrol acetate, risedronate, pamidronate, ibandronate, alendronate, denosumab, zoledronate, trastuzumab, tykerb, anthracyclines (e.g., daunorubicin and doxorubicin), bevacizumab, oxaliplatin, melphalan, etoposide, mechlorethamine, bleomycin, microtubule poisons, annonaceous acetogenins, or combinations thereof.

[0274] In another aspect, the antibodies of the present technology may be separately, sequentially or simultaneously administered with one or more therapeutic agents useful in the treatment of Alzheimer's disease. Examples of such therapeutic agents include acetylcholine esterase inhibitors such as tacrine (tetrahydroaminoacridine), donepezil hydrochloride, and rivastigmine; gamma-secretase inhibitors; anti-inflammatory agents such as cyclooxygenase II inhibitors; antioxidants such as Vitamin E and ginkolides; immunological approaches, such as, for example, immunization with A beta peptide or administration of anti-A beta peptide antibodies; statins; and direct or indirect neurotropic agents such as Cerebrolysin®, AIT-082 (Emilieu, 2000, *Arch. Neurol.* 57:454).

[0275] The compositions of the present technology may optionally be administered as a single bolus to a subject in need thereof. Alternatively, the dosing regimen may comprise multiple administrations performed at various times after the appearance of tumors or amyloid plaques.

[0276] Administration can be carried out by any suitable route, including orally, intranasally, parenterally (intravenously, intramuscularly, intraperitoneally, or subcutaneously), rectally, intracranially, intrathecally, or topically. Administration includes self-administration and the administration by another. It is also to be appreciated that the various modes of treatment of medical conditions as described are intended to mean "substantial", which includes total but also less than total treatment, and wherein some biologically or medically relevant result is achieved.

[0277] In some embodiments, the antibodies of the present technology comprise pharmaceutical formulations which may be administered to subjects in need thereof in one or more doses. Dosage regimens can be adjusted to provide the desired response (e.g., a therapeutic response).

[0278] Typically, an effective amount of the antibody compositions of the present technology, sufficient for achieving a therapeutic effect, range from about 0.000001 mg per kilogram body weight per day to about 10,000 mg per kilogram body weight per day. Typically, the dosage ranges are from about 0.0001 mg per kilogram body weight per day to about 100 mg per kilogram body weight per day. For administration of heterodimeric trivalent/tetravalent multispecific antibodies, the dosage ranges from about 0.0001 to 100 mg/kg, and more usually 0.01 to 5 mg/kg every week, every two weeks or every three weeks, of the subject body weight. For example, dosages can be 1 mg/kg body weight or 10 mg/kg body weight every week, every two weeks or every three weeks or within the range of 1-10 mg/kg every week, every two weeks or every three weeks. In one embodiment, a single dosage of antibody ranges from 0.1-10,000 micrograms per kg body weight. In one embodiment, antibody concentrations in a carrier range from 0.2 to 2000 micrograms per delivered milliliter. An exemplary treatment regime entails administration once per every two weeks or once a month or once every 3 to 6 months. Heterodimeric trivalent/tetravalent multispecific antibodies may be administered on multiple occasions. Intervals between single dosages can be hourly, daily, weekly, monthly or yearly. Intervals can also be irregular as indicated by measuring blood levels of the antibody in the subject. In some methods, dosage is adjusted to achieve a serum antibody concentration in the subject of from about 75 μg/mL to about 125 μg/mL, 100 μg/mL to about 150 μg/mL, from about 125 μg/mL to about 175 μg/mL, or from about 150 μg/mL to about 200 μg/mL. Alternatively, heterodimeric trivalent/tetravalent multispecific antibodies can be administered as a sustained release formulation, in which case less frequent administration is required. Dosage and frequency vary depending on the half-life of the antibody in the subject. The dosage and frequency of administration can vary depending on whether the treatment is prophylactic or therapeutic. In prophylactic applications, a relatively low dosage is administered at relatively infrequent intervals over a long period of time. In therapeutic applications, a relatively high dosage at relatively short intervals is sometimes required until progression of the disease is reduced or terminated, or until the subject shows partial or complete amelioration of symptoms of disease. Thereafter, the patient can be administered a prophylactic regime.

[0279] Toxicity. Optimally, an effective amount (e.g., dose) of heterodimeric trivalent/tetravalent multispecific antibody described herein will provide therapeutic benefit without causing substantial toxicity to the subject. Toxicity of the heterodimeric trivalent/tetravalent multispecific antibody described herein can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., by determining the LD_{50} (the dose lethal to 50% of the population) or the LD_{100} (the dose lethal to 100% of the population). The dose ratio between toxic and therapeutic effect is the therapeutic index. The data obtained from these cell culture assays and animal studies can be used in formulating a dosage range that is not toxic for use in human. The dosage of the heterodimeric trivalent/tetravalent multispecific antibody described herein lies within a range of circulating concentrations that include the effective dose with little or no toxicity. The dosage can vary within this range depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the subject's condition. See, e.g., Fingl et al., In: *The Pharmacological Basis of Therapeutics*, Ch. 1 (1975).

Formulations of Pharmaceutical Compositions

[0280] Formulations of Pharmaceutical Compositions. According to the methods of the present technology, the heterodimeric trivalent/tetravalent multispecific antibodies can be incorporated into pharmaceutical compositions suitable for administration. The pharmaceutical compositions

generally comprise recombinant or substantially purified antibody and a pharmaceutically-acceptable carrier in a form suitable for administration to a subject. Pharmaceutically-acceptable carriers are determined in part by the particular composition being administered, as well as by the particular method used to administer the composition. Accordingly, there is a wide variety of suitable formulations of pharmaceutical compositions for administering the antibody compositions (See, e.g., *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, Pa. 18th ed., 1990). The pharmaceutical compositions are generally formulated as sterile, substantially isotonic and in full compliance with all Good Manufacturing Practice (GMP) regulations of the U.S. Food and Drug Administration.

[0281] The terms "pharmaceutically-acceptable," "physiologically-tolerable," and grammatical variations thereof, as they refer to compositions, carriers, diluents and reagents, are used interchangeably and represent that the materials are capable of administration to a subject without the production of undesirable physiological effects to a degree that would prohibit administration of the composition. For example, "pharmaceutically-acceptable excipient" means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic, and desirable, and includes excipients that are acceptable for veterinary use as well as for human pharmaceutical use. Such excipients can be solid, liquid, semisolid, or, in the case of an aerosol composition, gaseous. "Pharmaceutically-acceptable salts and esters" means salts and esters that are pharmaceutically-acceptable and have the desired pharmacological properties. Such salts include salts that can be formed where acidic protons present in the composition are capable of reacting with inorganic or organic bases. Suitable inorganic salts include those formed with the alkali metals, e.g., sodium and potassium, magnesium, calcium, and aluminum. Suitable organic salts include those formed with organic bases such as the amine bases, e.g., ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like. Such salts also include acid addition salts formed with inorganic acids (e.g., hydrochloric and hydrobromic acids) and organic acids (e.g., acetic acid, citric acid, maleic acid, and the alkane- and arene-sulfonic acids such as methanesulfonic acid and benzenesulfonic acid). Pharmaceutically-acceptable esters include esters formed from carboxy, sulfonyloxy, and phosphonoxy groups present in the heterodimeric trivalent/tetravalent multispecific antibody, e.g., C1-6 alkyl esters. When there are two acidic groups present, a pharmaceutically-acceptable salt or ester can be a mono-acid-mono-salt or ester or a di-salt or ester; and similarly where there are more than two acidic groups present, some or all of such groups can be salified or esterified. A heterodimeric trivalent/tetravalent multispecific antibody named in this technology can be present in unsalified or unesterified form, or in salified and/or esterified form, and the naming of such heterodimeric trivalent/tetravalent multispecific antibody is intended to include both the original (unsalified and unesterified) compound and its pharmaceutically-acceptable salts and esters. Also, certain embodiments of the present technology can be present in more than one stereoisomeric form, and the naming of such heterodimeric trivalent/tetravalent multispecific antibody is intended to include all single stereoisomers and all mixtures (whether racemic or otherwise) of such stereoisomers. A person of ordinary skill in the art, would have no difficulty determining the appropriate timing, sequence and dosages of administration for particular drugs and compositions of the present technology.

[0282] Examples of such carriers or diluents include, but are not limited to, water, saline, Ringer's solutions, dextrose solution, and 5% human serum albumin. Liposomes and non-aqueous vehicles such as fixed oils may also be used. The use of such media and compounds for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or compound is incompatible with the heterodimeric trivalent/tetravalent multispecific antibody, use thereof in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

[0283] A pharmaceutical composition of the present technology is formulated to be compatible with its intended route of administration. The heterodimeric trivalent/tetravalent multispecific antibody compositions of the present technology can be administered by parenteral, topical, intravenous, oral, subcutaneous, intraarterial, intradermal, transdermal, rectal, intracranial, intrathecal, intraperitoneal, intranasal; or intramuscular routes, or as inhalants. The heterodimeric trivalent/tetravalent multispecific antibody can optionally be administered in combination with other agents that are at least partly effective in treating a disease or medical condition described herein.

[0284] Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial compounds such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating compounds such as ethylenediaminetetraacetic acid (EDTA); buffers such as acetates, citrates or phosphates, and compounds for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[0285] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringeability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, e.g., water, ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, e.g., by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal compounds, e.g., parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be desirable to include isotonic compounds, e.g., sugars, polyalcohols such as manitol, sorbitol, sodium chloride in

the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition a compound which delays absorption, e.g., aluminum monostearate and gelatin.

[0286] Sterile injectable solutions can be prepared by incorporating a heterodimeric trivalent/tetravalent multispecific antibody of the present technology in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the heterodimeric trivalent/tetravalent multispecific antibody into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof. The antibodies of the present technology can be administered in the form of a depot injection or implant preparation which can be formulated in such a manner as to permit a sustained or pulsatile release of the active ingredient.

[0287] Oral compositions generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the heterodimeric trivalent/tetravalent multispecific antibody can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding compounds, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating compound such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening compound such as sucrose or saccharin; or a flavoring compound such as peppermint, methyl salicylate, or orange flavoring.

[0288] For administration by inhalation, the heterodimeric trivalent/tetravalent multispecific antibody is delivered in the form of an aerosol spray from pressured container or dispenser which contains a suitable propellant, e.g., a gas such as carbon dioxide, or a nebulizer.

[0289] Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, e.g., for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the heterodimeric trivalent/tetravalent multispecific antibody is formulated into ointments, salves, gels, or creams as generally known in the art.

[0290] The heterodimeric trivalent/tetravalent multispecific antibody can also be prepared as pharmaceutical compositions in the form of suppositories (e.g., with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

[0291] In one embodiment, the heterodimeric trivalent/tetravalent multispecific antibody is prepared with carriers that will protect the heterodimeric trivalent/tetravalent multispecific antibody against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically-acceptable carriers. These can be prepared according to methods known to those skilled in the art, e.g., as described in U.S. Pat. No. 4,522,811.

Kits

[0292] The present technology provides kits for the detection and/or treatment of cancer, comprising at least one heterodimeric trivalent/tetravalent multispecific antibody composition described herein, or a functional variant (e.g., substitutional variant) thereof. Optionally, the above described components of the kits of the present technology are packed in suitable containers and labeled for diagnosis and/or treatment of cancer. The above-mentioned components may be stored in unit or multi-dose containers, for example, sealed ampoules, vials, bottles, syringes, and test tubes, as an aqueous, preferably sterile, solution or as a lyophilized, preferably sterile, formulation for reconstitution. The kit may further comprise a second container which holds a diluent suitable for diluting the pharmaceutical composition towards a higher volume. Suitable diluents include, but are not limited to, the pharmaceutically acceptable excipient of the pharmaceutical composition and a saline solution. Furthermore, the kit may comprise instructions for diluting the pharmaceutical composition and/or instructions for administering the pharmaceutical composition, whether diluted or not. The containers may be formed from a variety of materials such as glass or plastic and may have a sterile access port (for example, the container may be an intravenous solution bag or a vial having a stopper which may be pierced by a hypodermic injection needle). The kit may further comprise more containers comprising a pharmaceutically acceptable buffer, such as phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, syringes, culture medium for one or more of the suitable hosts. The kits may optionally include instructions customarily included in commercial packages of therapeutic or diagnostic products, that contain information about, for example, the indications, usage, dosage, manufacture, administration, contraindications and/or warnings concerning the use of such therapeutic or diagnostic products.

[0293] The kits are useful for detecting the presence of a target antigen in a biological sample, e.g., any body fluid including, but not limited to, e.g., serum, plasma, lymph, cystic fluid, urine, stool, cerebrospinal fluid, ascitic fluid or blood and including biopsy samples of body tissue. For example, the kit can comprise: one or more heterodimeric

trivalent/tetravalent multispecific antibodies of the present technology capable of binding a target antigen in a biological sample; means for determining the amount of the target antigen in the sample; and means for comparing the amount of the immunoreactive target antigen in the sample with a standard. One or more of the heterodimeric trivalent/tetravalent multispecific antibodies may be labeled. The kit components, (e.g., reagents) can be packaged in a suitable container. The kit can further comprise instructions for using the kit to detect the immunoreactive target antigen.

[0294] For antibody-based kits, the kit can comprise, e.g., 1) a first antibody, e.g. a humanized, or chimeric heterodimeric trivalent/tetravalent multispecific antibody of the present technology, attached to a solid support, which binds to a target antigen; and, optionally; 2) a second, different antibody which binds to either the target antigen or to the first antibody, and is conjugated to a detectable label.

[0295] The kit can also comprise, e.g., a buffering agent, a preservative or a protein-stabilizing agent. The kit can further comprise components necessary for detecting the detectable-label, e.g., an enzyme or a substrate. The kit can also contain a control sample or a series of control samples, which can be assayed and compared to the test sample. Each component of the kit can be enclosed within an individual container and all of the various containers can be within a single package, along with instructions for interpreting the results of the assays performed using the kit. The kits of the present technology may contain a written product on or in the kit container. The written product describes how to use the reagents contained in the kit, e.g., for detection of a target antigen in vitro or in vivo, or for treatment of cancer in a subject in need thereof. In certain embodiments, the use of the reagents can be according to the methods of the present technology.

EXAMPLES

[0296] The present technology is further illustrated by the following Examples, which should not be construed as limiting in any way.

Example 1: Materials and Methods

[0297] Protein production. All proteins were expressed using the expi293 expression system (Thermo Fisher Scientific, Waltham Mass.) according to manufacturer's instructions. Briefly, maxiprepped plasmids containing each antibody were diluted and incubated with expifectamine for 20 min before being added to expi293s in shaker flasks. Cells were incubated for 4 days or until cell viability dropped <70%, whichever came first. IgG-based proteins were purified over a protein A column using a GE P920 AKTA FPLC and eluted using 50 mM Citric acid. The BiTE was purified using prepacked Ni^{2+}NTA columns (GE) and eluted using a 250 mM imidazole buffer. All proteins were run on SEC-HPLC to validate their size and quantify their purity.

[0298] Heterodimerization. Heterodimerization was achieved using Fab Arm Exchange (FAE). Briefly, K409R and F405L mutations were placed in the Fc regions of each reciprocal pair of IgG or IgG-[L]-scFv bispecific antibodies to be heterodimerized. Paired homodimers were then mixed at 3 different molar rations (1:1, 1.2:1 and 1:1.2) and incubated in reducing conditions for 5 hrs at 30° C. before being dialyzed overnight at room temperature in sodium citrate buffer (pH 8.2). After an initial overnight dialysis, samples were moved to 4° C. for another 24 hrs before being analyzed by SEC-HPLC and CZE chromatography to assess heterodimerization yields. In all experiments the 1:1 ratio was used, after validating its purity was optimal.

[0299] Cell lines. EL.4 cells were obtained from ATCC. M14 cells were obtained from ATCC and transfected with luciferase prior to use in all assays. IMR32 cells were obtained from ATCC and transfected with luciferase prior to use in all assays. Molm13-fluc cells were a gift from the Brentjens lab. Naïve T-cells were purified from PBMCs using the Dynabeads™ Untouched™ human T cells kit, according to manufacturer's protocol. Activated T cells were generated by using CD3/CD28 dynabeads and 30U/ml of human IL-2. T-cells were stimulated twice, at day 0 and day 7, and used in cytotoxicity, cell binding or conjugate assays day 15-18 of culture.

[0300] Cell binding FACS. For cell binding assays, 1M cells were incubated with 5 pmol of antibody for 30 min at 4° C., followed by either an anti-human Fc secondary or an anti-3F8 or anti-OKT3 idiotype antibody (5 pmol) and the corresponding anti-Fc secondary (anti-rat APC or anti-mouse PE, respectively). Samples were acquired using a FACSCalibur and analyzed by FlowJo.

[0301] Affinity Measurements. Binding kinetics were evaluated using SPR (GE, Biacore T200). Briefly, chips were coated with GD2, CD33 or huCD3de antigen and a titration series of each bispecific antibody were flowed over them. Binding affinities were calculated using a two-state reaction model.

[0302] Cytotoxicity measurements. Cytotoxicity was evaluated using a 4 hr ^{51}Cr release assay. Briefly, 1M target cells were incubated with 100 μCi of activity and incubated with activated human T cells (10:1 E:T) and serially titrated bispecific antibody. Released ^{51}Cr was measured using a gamma counter.

[0303] Animal Models. All experiments have been conducted in accordance with and approved by the Institutional Animal Care and Use Committee in MSKCC. Two mouse models were used: (1) a humanized immunodeficient xenograft model (huDKO) and (2) a transgenic huCD3e-expressing syngeneic model (huCD3e-tg). Briefly, huDKO (Balb/C IL2rg$^{-/-}$, Rag2$^{-/-}$) mice were implanted subcutaneously with 2M M14 melanoma cells. After 5-15 days, mice were treated with intravenous activated human T cells (20-40M/dose), intravenous bispecific antibody (25 pmol/dose) and subcutaneous IL-2 (100U/dose) for three weeks. For huCD3e-tg (C57BL/6) mice were implanted subcutaneously with EL.4 lymphoma cells. After 7 days, mice were treated intravenous bispecific antibody (25 pmol/dose) for three weeks. For BiTEs, either 7 pmol or 350 pmol were administered daily for 3 weeks. Weights and tumor volumes were measured once per week and overall mouse health was evaluated at least 3-times per week. Mice were sacrificed if tumor volumes reached 1.5-2.0 cm^3 volumes. No toxicities were seen during treatment of any mice.

[0304] Conjugate formation. For conjugate assays, T cells were labeled with CFSE (2.5 μM) and M14 melanoma cells were labeled with CTV (2.5 μM). 50 M/ml cells were incubated with dye for 5 min at room temperature, followed by the addition of 30 ml of complete RPMI (supplemented with 10% fetal calf serum (heat inactivated), 2 mM glutamine and 1% P/S) and incubated at 37° C. for 20 min. Cells were pelleted and washed with complete medium twice

before being added antibodies or cells. Labeled cells were mixed at a 1:5 ratio (E:T) along with serially titrated bispecific antibody, in duplicate. After 30 min, cells were fixed with a final concentration of 2% PFA (10 min, RT) and washed in 5 ml of PBS. Cells were acquired using a BD LSR Fortessa and analyzed using Flowjo.

[0305] Activation assay. Purified naïve T cells were incubated with M14 melanoma cells (10:1 E:T) and serially titrated bispecific antibody, in duplicate. After 24 hrs supernatant was collected and frozen at −80° C. Cells were then stained with antibodies against CD4, CD8, CD45, and CD69 to assess the CD69 upregulation. For the 96 hr assay, T cells were first labeled with 2.504 of CTV. After 96 hrs cells were stained with antibodies against CD4, CD8, CD45 and CD25 to assess CD25 upregulation and CTV dilution.

[0306] Cytokine Assay. Frozen supernatant from the activation assay (24 hr) was used to quantify cytokine production after 24 hrs of coculture. IL-2, IFNγ, IL-10, IL-6 and TNFα were measured with the 5-plex legend plex system according to manufacturer guidelines.

[0307] FIG. **23** provides a summary of the various HDTVS antibodies tested in the Examples disclosed herein. The table summarizes all successfully produced HDTVS formatted multi-specific antibodies across a variety of antigen models. All clones were expressed in Expi293 cells and heterodimerized using the controlled Fab Arm Exchange method. HDTVS type displays the category of each clone. Fab 1 and scFv 1 (and corresponding Ag1 and Ag3) are attached in a cis-orientation on one heavy chain (linked by the light chain of Fab) while Fab 2 and scFv 2 (and corresponding Ag2 and Ag4) are on a separate heavy chain molecule in a cis-orientation (linked by the light chain of Fab).

[0308] Sequences. The amino acid sequences utilized in the Examples are provided below:

Anti-HER2
LC(VL-CL-scFv)
(SEQ ID NO: 2353)
DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYS

ASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQ

GTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV

DNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG

LSSPVTKSFNRGECTSGGGGSGGGGSGGGGSQVQLVQSGGGVVQPGRSLR

LSCKASGYTFTRYTIVIRWVRQAPGKCLEWIGYINPSRGYTNYNQKFKDR

FTISRDNSKNTAFLQMDSLRPEDTGVYFCARYYDDHYSLDYWGQGTPVTV

SSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDR

VTITCSASSSVSYMNWYQQTPGKAPKRWIYDTSKLASGVPSRFSGSGSGT

DYTFTISSLQPEDIATYYCQQWSSNPFTFGCGTKLQITR

HC(VH-CH1-CH2-CH3, N297A, K322A):
(SEQ ID NO: 2354)
EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVAR

TYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWG

GDGFYAMDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK

DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT

-continued

YICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKP

KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYA

STYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQ

VYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV

LDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

HC(VH-CH1-CH2-CH3, N297A, K322A, F405L):
(SEQ ID NO: 2355)
EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVAR

TYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWG

GDGFYAMDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK

DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT

YICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKP

KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYA

STYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQ

VYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV

LDSDGSFLLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

HC(VH-CH1-CH2-CH3, N297A, K322A, K409R):
(SEQ ID NO: 2356)
EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVAR

TYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWG

GDGFYAMDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK

DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT

YICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKP

KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYA

STYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQ

VYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV

LDSDGSFFLYSRLTVDKSRWQQGNVFScSVMHEALHNHYTQKSLSLSPGK

Anti-GD2
LC(VL-CL-scFv):
(SEQ ID NO: 2357)
EIVMTQTPATLSVSAGERVTITCKASQSVSNDVTWYQQKPGQAPRLLIYS

ASNRYSGVPARFSGSGYGTEFTFTISSVQSEDFAVYFCQQDYSSFGQGTK

LEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNA

LQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSS

PVTKSFNRGECTSGGGGSGGGGSGGGGSQVQLVQSGGGVVQPGRSLRLSC

KASGYTFTRYTMHWVRQAPGKCLEWIGYINPSRGYTNYNQKFKDRFTISR

DNSKNTAFLQMDSLRPEDTGVYFCARYYDDHYSLDYWGQGTPVTVSSGGG

GSGGGGSGGGGSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITC

SASSSVSYMNWYQQTPGKAPKRWIYDTSKLASGVPSRFSGSGSGTDYTFT

ISSLQPEDIATYYCQQWSSNPFTFGCGTKLQITR

LC(VL-CL):
(SEQ ID NO: 2358)
EIVMTQTPATLSVSAGERVTITCKASQSVSNDVTWYQQKPGQAPRLLIYS

ASNRYSGVPARFSGSGYGTEFTFTISSVQSEDFAVYFCQQDYSSFGQGTK

-continued

LEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNA

LQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSS

PVTKSFNRGEC

HC(VH-CH1-CH2-CH3, N297A, K322A):

(SEQ ID NO: 2359)

QVQLVESGPGVVQPGRSLRISCAVSGFSVTNYGVHWVRQPPGKGLEWLGV

IWAGGITNYNSAFMSRLTISKDNSKNTVYLQMNSLRAEDTAMYYCASRGG

HYGYALDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD

YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY

ICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPK

DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYAS

TYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQV

YTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL

DSDGSFFLYSKLTVDKSRWQQGNVFScSVMHEALHNHYTQKSLSLSPGK

HC(VH-CH1-CH2-CH3, N297A, K322A, F405L):

(SEQ ID NO: 2360)

QVQLVESGPGVVQPGRSLRISCAVSGFSVTNYGVHWVRQPPGKGLEWLGV

IWAGGITNYNSAFMSRLTISKDNSKNTVYLQMNSLRAEDTAMYYCASRGG

HYGYALDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD

YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY

ICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPK

DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYAS

TYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQV

YTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL

DSDGSFLLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

HC(VH-CH1-CH2-CH3, N297A, K322A, K409R):

(SEQ ID NO: 2361)

QVQLVESGPGVVQPGRSLRISCAVSGFSVTNYGVHWVRQPPGKGLEWLGV

IWAGGITNYNSAFMSRLTISKDNSKNTVYLQMNSLRAEDTAMYYCASRGG

HYGYALDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD

YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY

ICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPK

DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYAS

TYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQV

YTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL

DSDGSFFLYSRLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Anti-GD2(2)

LC(VL-CL-scFv):

(SEQ ID NO: 2362)

KIVMTQTPATLSVSAGERVTITCKASQSVSNHVTWYQQKPGQAPRLLIYS

ASNRYSGVPARFSGSGYGTEFTFTISSVQSEDFAVYFCQQDYSSFGQGTK

LEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNA

LQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSS

-continued

PVTKSFNRGECTSGGGGSGGGGSGGGGSQVQLVQSGGGVVQPGRSLRLSC

KASGYTFTRYTMHWVRQAPGKCLEWIGYINPSRGYTNYNQKFKDRFTISR

DNSKNTAFLQMDSLRPEDTGVYFCARYYDDHYSLDYWGQGTPVTVSSGGG

GSGGGGSGGGGSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITC

SASSSVSYMNWYQQTPGKAPKRWIYDTSKLASGVPSRFSGSGSGTDYTFT

ISSLQPEDIATYYCQQWSSNPFTFGCGTKLQITR

LC(VL-CL):

(SEQ ID NO: 2363)

KIVMTQTPATLSVSAGERVTITCKASQSVSNHVTWYQQKPGQAPRLLIYS

ASNRYSGVPARFSGSGYGTEFTFTISSVQSEDFAVYFCQQDYSSFGQGTK

LEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNA

LQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSS

PVTKSFNRGEC

HC(VH-CH1-CH2-CH3, N297A, K322A):

(SEQ ID NO: 2364)

QVQLVESGPGVVQPGRSLRISCAVSGFSVTNYGVHWVRQPPGKGLEWLGV

IWAGGITNYNSAFMSRLTISKDNSKNTVYLQMNSLRAEDTAMYYCASRGG

HYGYALDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD

YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY

ICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPK

DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYAS

TYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQV

YTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL

DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

HC(VH-CH1-CH2-CH3, N297A, K322A, F405L):

(SEQ ID NO: 2365)

QVQLVESGPGVVQPGRSLRISCAVSGFSVTNYGVHWVRQPPGKGLEWLGV

IWAGGITNYNSAFMSRLTISKDNSKNTVYLQMNSLRAEDTAMYYCASRGG

HYGYALDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD

YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY

ICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPK

DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYAS

TYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQV

YTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL

DSDGSFLLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

HC(VH-CH1-CH2-CH3, N297A, K322A, K409R):

(SEQ ID NO: 2366)

QVQLVESGPGVVQPGRSLRISCAVSGFSVTNYGVHWVRQPPGKGLEWLGV

IWAGGITNYNSAFMSRLTISKDNSKNTVYLQMNSLRAEDTAMYYCASRGG

HYGYALDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD

YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY

ICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPK

DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYAS

-continued

TYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQV

YTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL

DSDGSFFLYSRLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Anti-GD2(3)
LC(VL-CL-scFv):

(SEQ ID NO: 2367)

EIVMTQSPATLSVSPGERATLSCRSSQSLVHRNGNTYLHWYLQKPGQSPK

LLIHKVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDLGVYFCSQSTHVP

PLTFGAGTKLELKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA

KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYAC

EVTHQGLSSPVTKSFNRGECTSGGGGSGGGGSGGGGSQVQLVQSGGGVVQ

PGRSLRLSCKASGYTFTRYTMHWVRQAPGKCLEWIGYINPSRGYTNYNQK

FKDRFTISRDNSKNTAFLQMDSLRPEDTGVYFCARYYDDHYSLDYWGQGT

PVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSDIQMTQSPSSLSAS

VGDRVTITCSASSSVSYMNWYQQTPGKAPKRWIYDTSKLASGVPSRFSGS

GSGTDYTFTISSLQPEDIATYYCQQWSSNPFTFGCGTKLQITR

LC(VL-CL):

(SEQ ID NO: 2368)

EIVMTQSPATLSVSPGERATLSCRSSQSLVHRNGNTYLHWYLQKPGQSPK

LLIHKVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDLGVYFCSQSTHVP

PLTFGAGTKLELKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA

KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYAC

EVTHQGLSSPVTKSFNRGEC

HC(VH-CH1-CH2-CH3, N297A, K322A):

(SEQ ID NO: 2369)

EVQLLQSGPELEKPGASVMISCKASGSSFTGYNMNWVRQNIGKSLEWIGA

IDPYYGGTSYNQKFKGRATLTVDKSSSTAYMHLKSLTSEDSAVYYCVSGM

EYWGQGTSVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV

TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH

KPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMIS

RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVS

VLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQVYTLPPS

RDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF

FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

HC(VH-CH1-CH2-CH3, N297A, K322A, F405L):

(SEQ ID NO: 2370)

EVQLLQSGPELEKPGASVMISCKASGSSFTGYNMNWVRQNIGKSLEWIGA

IDPYYGGTSYNQKFKGRATLTVDKSSSTAYMHLKSLTSEDSAVYYCVSGM

EYWGQGTSVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV

TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH

KPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMIS

RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVS

VLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQVYTLPPS

-continued

RDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF

LLYSKLTVDKSRWQQGNVFScSVMHEALHNHYTQKSLSLSPGK

HC(VH-CH1-CH2-CH3, N297A, K322A, K409R):

(SEQ ID NO: 2371)

EVQLLQSGPELEKPGASVMISCKASGSSFTGYNMNWVRQNIGKSLEWIGA

IDPYYGGTSYNQKFKGRATLTVDKSSSTAYMHLKSLTSEDSAVYYCVSGM

EYWGQGTSVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV

TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH

KPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMIS

RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVS

VLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQVYTLPPS

RDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF

FLYSRLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Anti-CD33
LC(VL-CL-scFv):

(SEQ ID NO: 2372)

EIVLTQSPATLSVSLGERATISCRASESVDNYGISFMNWFQQKPGQPPRL

LIYAASNQGSGVPARFSGSGPGTDFTLTISSMEPEDFAMYFCQQSKEVPW

TFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV

QWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEV

THQGLSSPVTKSFNRGECTSGGGGSGGGGSGGGGSQVQLVQSGGGVVQPG

RSLRLSCKASGYTFTRYTMHWVRQAPGKCLEWIGYINPSRGYTNYNQKFK

DRFTISRDNSKNTAFLQMDSLRPEDTGVYFCARYYDDHYSLDYWGQGTPV

TVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVG

DRVTITCSASSSVSYMNWYQQTPGKAPKRWIYDTSKLASGVPSRFSGSGS

GTDYTFTISSLQPEDIATYYCQQWSSNPFTFGCGTKLQITR

LC(VL-CL):

(SEQ ID NO: 2373)

EIVLTQSPATLSVSLGERATISCRASESVDNYGISFMNWFQQKPGQPPRL

LIYAASNQGSGVPARFSGSGPGTDFTLTISSMEPEDFAMYFCQQSKEVPW

TFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV

QWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEV

THQGLSSPVTKSFNRGEC

HC(VH-CH1-CH2-CH3, N297A, K322A):

(SEQ ID NO: 2374)

EVQLVQSGPEVVKPGASVKISCKASGYTFTDYNMHWVRQAHGQSLEWIGY

IYPYNGGTGYNQKFKSRATLTVDNSASTAYMEVSSLRSEDTAVYYCARGR

PAMDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP

EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICN

VNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTL

MISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYR

VVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQVYTL

-continued

PPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD

GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

HC(VH-CH1-CH2-CH3, N297A, K322A, F405L):

(SEQ ID NO: 2375)

EVQLVQSGPEVVKPGASVKISCKASGYTFTDYNMHWVRQAHGQSLEWIGY

IYPYNGGTGYNQKFKSRATLTVDNSASTAYMEVSSLRSEDTAVYYCARGR

PAMDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP

EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICN

VNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTL

MISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYR

VVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQVYTL

PPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD

GSFLLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

HC(VH-CH1-CH2-CH3, N297A, K322A, K409R):

(SEQ ID NO: 2376)

EVQLVQSGPEVVKPGASVKISCKASGYTFTDYNMHWVRQAHGQSLEWIGY

IYPYNGGTGYNQKFKSRATLTVDNSASTAYMEVSSLRSEDTAVYYCARGR

PAMDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP

EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICN

VNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTL

MISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYR

VVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQVYTL

PPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD

GSFFLYSRLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Anti-CD3

LC(VL-CL):

(SEQ ID NO: 2377)

DIQMTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQTPGKAPKRWIYDT

SKLASGVPSRFSGSGSGTDYTFTISSLQPEDIATYYCQQWSSNPFTFGQG

TKLQITRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVD

NALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGL

SSPVTKSFNRGEC

HC(VH-CH1-CH2-CH3, N297A, K322A):

(SEQ ID NO: 2378)

QVQLVQSGGGVVQPGRSLRLSCKASGYTFTRYTMHWVRQAPGKGLEWIGY

INPSRGYTNYNQKFKDRFTISRDNSKNTAFLQMDSLRPEDTGVYFCARYY

DDHYSLDYWGQGTPVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD

YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY

ICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPK

DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYAS

TYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQV

YTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL

DSDGSFFLYSKLTVDKSRWQQGNVFScSVMHEALHNHYTQKSLSLSPGK

-continued

HC(VH-CH1-CH2-CH3, N297A, K322A, F405L):

(SEQ ID NO: 2379)

QVQLVQSGGGVVQPGRSLRLSCKASGYTFTRYTMHWVRQAPGKGLEWIGY

INPSRGYTNYNQKFKDRFTISRDNSKNTAFLQMDSLRPEDTGVYFCARYY

DDHYSLDYWGQGTPVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD

YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY

ICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPK

DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYAS

TYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQV

YTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL

DSDGSFLLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

HC(VH-CH1-CH2-CH3, N297A, K322A, K409R):

(SEQ ID NO: 2380)

QVQLVQSGGGVVQPGRSLRLSCKASGYTFTRYTMHWVRQAPGKGLEWIGY

INPSRGYTNYNQKFKDRFTISRDNSKNTAFLQMDSLRPEDTGVYFCARYY

DDHYSLDYWGQGTPVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD

YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY

ICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPK

DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYAS

TYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQV

YTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL

DSDGSFFLYSRLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

huOKT3-VL

(SEQ ID NO: 2390)

DIQMTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQTPGKAPKRWIYDT

SKLASGVPSRFSGSGSGTDYTFTISSLQPEDIATYYCQQWSSNPFTFGCG

TKLQIT

huOKT3-VH

(SEQ ID NO: 2391)

QVQLVQSGGGVVQPGRSLRLSCKASGYTFTRYTMHWVRQAPGKCLEWIGY

INPSRGYTNYNQKFKDRFTISRDNSKNTAFLQMDSLRPEDTGVYFCARYY

DDHYSLDYWGQGTPVTVSS

huA33-VL

(SEQ ID NO: 2392)

DIQMTQSQSSLSTSVGDRVTITCKASQNVRTVVAWYQQKPGKSPKTLIYL

ASNRHTGVPSRFSGSGSGTEFTLTISNVQPEDFADYFCLQHWSYPLTFGS

GTKLEIK

huA33-VH

(SEQ ID NO: 2393)

EVQLVESGGGLVKPGGSLRLSCAASGFAFSTYDMSWVRQAPGKRLEWVAT

ISSGGSYTYYLDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAPTT

VVPFAYWGQGTLVTVSS

-continued

huM195-VL

(SEQ ID NO: 2394)

EIVLTQSPATLSVSLGERATISCRASESVDNYGISFMNWFQQKPGQPPRL

LIYAASNQGSGVPARFSGSGPGTDFTLTISSMEPEDFAMYFCQQSKEVPW

TFGGGTKLEIK

huM195-VH

(SEQ ID NO: 2395)

EVQLVQSGPEVVKPGASVKISCKASGYTFTDYNMHWVRQAHGQSLEWIGY

IYPYNGGTGYNQKFKSRATLTVDNSASTAYMEVSSLRSEDTAVYYCARGR

PAMDYWGQGTLVTVSS

Example 2: Functionality of Lo1+1+2, Hi1+1+1 and 2+1+1 HDTVS Variants

[0309] FIG. **1***a* shows the basic design strategy of each HDTVS variant compared with the parental 2+2 IgG-[L]-scFv. FIGS. **1***b*-**1***g* describe each of the three designs in more detail.

[0310] The Lo1+1+2 utilizes two different Fab domains that (a) target two distinct antigens within a tumor and (b) have moderate to low binding affinities (e.g. K_D 100 nM-100 pM), and two identical scFvs that target an immune cell so as to improve tumor cell specificity. As illustrated in FIG. **1***b*, this design targets tumors more specifically due to its unexpectedly poor activity when only one of the two Fab domains is engaged with the tumor target (such as when only one of the two Fab domain-specific antigens is expressed). Importantly, when both Fab domains bind their respective tumor targets, normal cytotoxic potency is restored. This allows for improved therapeutic index (or safety) when the target antigens are not unique to the tumor, where each target antigen (but never both) is shared to some extent by normal cells. While a standard BsAb or 2+2 design would harm normal tissues, this Lo1+1+2 design should spare normal tissues that express only one of the two targeted antigens, while maintaining the full potency against a tumor cell that expresses both antigens.

[0311] As illustrated in FIG. **1***c*, the Hi1+1+2 design is capable of recognizing two distinct antigens with equal potency, regardless of simultaneous binding. Since Fab domains of appropriately high affinity (e.g., K_D<100 pM) are sufficient to induce potent cytotoxicity even monovalently, two different Fab domains can be used to broaden the tumor cell selectivity and permits targeting of heterogeneous tumors with a single drug.

[0312] The 2+1+1 design is capable of improved immune cell interactions by virtue of its dual specificity toward the immune cell, either improving activation or providing more selective activation. As demonstrated herein, the second scFv domain is somewhat dispensable due to the biophysical properties of the IgG-[L]-scFv platform. Thus, using two different scFv domains can provide a greater diversity of interactions than a normal bivalent approach. As illustrated in FIG. **1***d*, the 2+1+1 design can be used to both improve signaling in a more selective population of immune cells (B1(+)B2(+)) or to enhance activation through colocalization of complementary pairs of receptors. Importantly, the 2+1+1 design can be used to interact with activating receptors and/or inhibitory receptors or antagonistic antibodies that specifically inhibit signaling of certain immune cell pathways, such as blocking PD-1 on T cells while activating through CD3.

[0313] The 2+1+1 design takes advantage of the two anti-immune cell binding domains to recruit a broader selection of immune cells (e.g., anti-CD3 for T cells+anti-CD16 for NK cells) or for combinatorial recruitment of payloads with immune cells as theranostics (e.g., anti-CD3 for T cells and anti-BnDOTA for imaging). As illustrated in FIG. **1***e*, the 2+1+1 design takes advantage of the minimal differences in therapeutic activity between a 2+1 design and a 2+2 design to add a new function, thus broadening the selection of delivered anti-tumor activity to multiple types of immune cells or to chemical or radiological payloads.

[0314] The 1+1+1+1 format combines the previous 4 designs to take advantage of all possible combinations. As shown in Figure if, this allows for the combinatorial properties of the 2+1+1 design to be combined with the specificity or selectivity improvements from the Hi1+1+2 and Lo1+1+2 designs.

Example 3: —Superiority of 2+2 IgG-[L]-scFv Design over BITE and IgG-Het

[0315] FIG. **2***a*-**2***b* show the unexpected benefits of the IgG-[L]-scFv (2+2 BsAb) over other common designs such as IgG-Het and BiTE, highlighting both the benefit of having a valency >1 and the structural properties imparted by a Fab/scFv combination. As shown in FIG. **2***a*, the top panels compare cytotoxicity, cell binding and antigen affinity properties between the IgG-[L]-scFv, IgG-Het and BiTE formats.

[0316] The left most panel shows that the 2+2 BsAb achieved nearly 1,000-fold improved cytotoxicity over the 1+1 IgG-Het and >20-fold than the 1+1 BiTE. Measurements were made using a standard four hour ^{51}Cr release assay using activated human T cells and GD2(+) M14-luciferase cells, with each antibody diluted over 7-logs. The center panel shows the varying levels of antigen binding (GD2 or CD3) between these three formats using GD2(+) M14-luciferase cells or CD3(+) activated human T cells. Cells were stained with each of the three formats and detected using either anti-hu3F8 or anti-huOKT3 idiotypic antibodies. As with the cytotoxicity, the cell binding to both antigens was superior for the 2+2 BsAb due to increased valency. The right panel displays the binding kinetics against the antigen GD2 for each of the three platforms. The 2+2 BsAb exhibited stronger antigen binding over either 1+1 design (BITE or IgG-Het). The bottom panels compare these three constructs in two separate animal models: a huCD3(+) transgenic syngeneic mouse model (left panel) or a humanized immunodeficient xenograft mouse model (right panel). Both models had antibodies injected twice per week and began approximately one week after tumor implantation. Only the 2+2 BsAb was capable of delaying subcutaneous GD2(+) EL.4 tumor growth in the syngeneic model. The 1+1 IgG-Het and the 1+1 BiTE were just as ineffective as the inactive negative control BsAb. Administering the BiTE format daily or at a 10× higher dose level ("hi dose" group, syngeneic mice, FIG. **2***a*) did not result in any anti-tumor effect. In the xenograft model, where human ATCs and IL-2 were added to support T cell survival in all groups, the 1+1 IgG-Het still failed to show any benefit compared to the control, while the 2+2 BsAb strongly inhibited subcutaneous GD2(+) M14Luc tumors. As show in FIG. **2***b*, these striking differences in cytotoxicity between the IgG-[L]-scFv and

IgG-Het formats were reproducible using two additional anti-GD2 antibodies, suggesting that the effects were not specific to any one GD2 epitope.

[0317] These results demonstrate that the HDTVS antibodies disclosed herein are useful in methods for treating a disease or condition, such as cancer.

Example 4: Characterization of IgG-[L]-scFv HDTVS Variants

[0318] FIG. **3** describes the characterization of the IgG-[L]-scFv platform to identify the necessity and sufficiency of each binding domain as well as their relative impact on overall functional activity. Unexpectedly, the changes in valency did not entirely correlate with changes in functional output, suggesting a preference for tumor binding by the Fab domain over immune cell binding by the scFv domain, as well as a preference for cis-oriented domains over trans-oriented domains.

[0319] As illustrated in FIG. **3**, the four IgG-[L]-scFv variants display potencies somewhere between the parental 2+2 IgG-[L]-scFv (top left) and the IgG-Het (bottom right). The 2+1 BsAb (second from left) used heterodimerization to remove one of the two immune cell binding scFv domains yet functioned quite similarly to the parental 2+2 BsAb. Neutralization of the second tumor cell binding Fab domain to create a 1+2 BsAb (third from right) reduced the potency further, but unexpectedly additional removal of an scFv domain did not significantly change the potency, as long as the two remaining domains were in a Cis orientation (1+1C, third from left). Neutralization of the second tumor cell binding Fab was achieved by replacing it with a Fab that binds CD33, an antigen not found on tumor cells or T cells. Neutralization/removal of both the tumor binding Fab domain and the T cell engaging scFv domain in a Trans orientation (1+1T, second from right) caused the biggest drop in potency (equivalent to the IgG-Het), even lower than the 1+1C despite equivalent valency. These results demonstrate that orientation or spatial arrangements of the antigen binding domains are important determinants of therapeutic potency.

[0320] These results demonstrate that the HDTVS antibodies disclosed herein are useful in methods for treating a disease or condition, such as cancer.

Example 5: Modifications of the 2+2 IgG-[L]-scFv and Their Relative Binding Activities

[0321] FIG. **4** describes the binding activities of each IgG-[L]-scFv variant, compared to the parental 2(GD2)+2 (CD3) BsAb and the IgG-Het. Monovalency towards tumor (e.g. 1+2), was created by changing one of the 2 Fab domains to an irrelevant binder (i.e., a huCD33 targeting Fab). Monovalency (e.g. 2+1) towards T cells is created by removing one of the two scFv domains. As illustrated in FIG. **4**, bivalency improves antigen binding over monovalency (upper panels). Surface Plasmon Resonance was used to measure antigen binding kinetics against both GD2 coated chips (upper left) and CD3 coated chips (upper right). Briefly, each BsAb was serially titrated and flowed against each chip. Against GD2, the 2+2 BsAb and 2(GD2)+1(CD3) BsAb showed equivalent binding activities whereas the 1+1C, 1+1T, 1+2 and 1+1 IgG-Het all displayed inferior GD2 binding. Against CD3, the pattern was similar, with bivalency being superior over monovalency, but to a lesser extent (which may be attributable in part to the spatial restrictions of bivalent scFv binding compared to Fab binding). The 2+2 and 1+2 BsAb showed the strongest binding, while the 2+1, 1+1T and 1+1C exhibited inferior binding kinetics. The Fab binding domain of the IgG-Het appeared to show some benefit over a monovalent scFv, but this may result from the more stable sequence of a Fab domain compared with an scFv domain, where CH1/CL interactions are lacking. Compared to SPR, cell binding (measured as described in FIG. **2** but using a standard anti-Fc secondary antibody instead of using anti-idiotypic antibodies) showed similar results (bottom left). GD2 binding (left Y-axis) was the strongest in constructs with bivalency (2+2, 2+1), and less for constructs with monovalency (1+1T, 1+1C, 1+2 and IgG-Het). The same pattern was observed with CD3-specific cell binding (right Y-axis), with 2+2 and 1+2 binding being more effective than 2+1, 1+1T and 1+1C.

[0322] Similar to the CD3-specific SPR readings, the IgG-Het showed stronger Fab binding than scFv binding. Conjugate formation between targets and effector cells when mixed together with titrated BsAb (bottom right), showed much smaller differences between IgG-[L]-scFv variants. The 2+2 BsAb showed the most efficient conjugate formation activity, followed by the 2+1 BsAb and then all others (except control). These results demonstrate that after the removal of the second anti-effector cell scFv, all other changes to the IgG-[L]-scFv do not markedly reduce its capacity to conjugate effector target cells together, or that the small differences in cell binding activities do not impact conjugate formation or the stability of conjugate formation.

[0323] These results demonstrate that the HDTVS antibodies disclosed herein are useful in methods for treating a disease or condition, such as cancer.

Example 6: Modifications of the 2+2 IgG-[L]-scFv and their Relative Cytotoxicity

[0324] FIG. **5** describes the anti-tumor cytotoxicity of each IgG-[L]-scFv variant in vitro, across two GD2(+) cell lines. As illustrated in FIG. **5** and summarized in TABLE 2, the variants showed a wide range of cytotoxic potency (assays were performed as described in FIG. **2**).

TABLE 2

	K_D				Cytotoxic EC50	
	GD2	Fold Change	CD3	Fold Change	EC50	Fold Change
2 + 2	2.8 nM	—	10 nM	—	17 fM	—
2 + 1	2.5 nM	0.9	310 nM	30.1	106 fM	6.2
1 + 1C	30 nM	10.9	110 nM	11.0	292 fM	17.2
1 + 2	31 nM	11.3	11 nM	1.0	454 fM	26.7
1 + 1H	31 nM	11.4	70 nM	6.8	14 pM	823.5
1 + 1T	21 nM	7.7	88 nM	8.5	13 pM	764.7

[0325] Against both tumor cell lines, the 2+2 BsAb displayed the highest cytotoxic effect, followed by the 2+1 and then both 1+1C and 1+2. Interestingly, the 1+1T and IgG-Het (nearly 1,000-fold worse than 2+2) were nearly identical to each other, suggesting that: the cis-oriented binding domains provide superior killing activity compared to trans-oriented binding domains, and that a 2+1 interaction is superior to a 1+2 interaction. Despite the similarities of both the trans and cis oriented 1+1 variants having identical tumor cell binding, effector cell binding capacities, antigen

binding kinetics, and conjugate formation activity, the cis-trans orientations of these two constructs differ substantially in the functional output (50-fold) as measured by in vitro cytotoxicity. This unexpected observation may account for why the 1+2 fails to kill as potently as the 2+1. Without wishing to be bound by theory, it is believed that the 1+2 interaction may be caught between a cis and trans interaction at all times, while the 2+1 is more often in a cis interaction. An alternative possibility is that the tumor-binding Fab domains may be more critical for driving anti-tumor potency.

[0326] Additionally, the value of each domain and its orientation was quantified. While the 2+2 was about 1,000-fold more potent than the IgG-Het (or 1+1T), it was only 6-fold more potent than the 2+1, and 20-25 fold more potent than the 1+2 or 1+1C. These data demonstrate that the second scFv imparts about 6-fold change in activity (2+2 is 6-fold better than 2+1), the bivalent Fab imparts about 25-fold change (2+2 is up to 25-fold better than 1+2 domain) and the Cis/Trans orientation imparts another 50-fold change (1+1C is 50-fold better than 1+1T).

[0327] These results demonstrate that the HDTVS antibodies disclosed herein are useful in methods for treating a disease or condition, such as cancer.

Example 7: Modifications of the 2+2 IgG-[L]-scFv and their Relative Immune Cell Activation

[0328] FIG. **6** describes the cell activation properties of each IgG-[L]-scFv variant in vitro. As illustrated in FIG. **6**, the variations made to the IgG-[L]-scFv variants significantly influence their capacity to activate immune cells. The upper panels show upregulation of CD69 expression on T cells after 24 hours of in vitro coculture with varying concentrations of each BsAb and GD2(+) M14Luc tumor cells. As in FIG. **5**, valency and cis/trans orientation appear to play an important role, suggesting that the activation potency and cytotoxicity are correlated. The 2+2 BsAb again displayed its superiority over all other variants tested, at both the level of expression level of CD69 (left) and the frequency of CD69(+) cells (right). Removal of a single domain (2+1 or 1+2) markedly lowered activation, and was made worse with the transition to 1+1C, 1+1T and finally IgG-Het. A similar pattern emerged after 96 hr of coculture (bottom panel). CD25 expression remained the highest for the 2+2, both in terms of expression level (left) and frequency of CD25(+) (center) cells. All other variants showed reduced activation of effector T cells. Proliferation was also measured using Cell Trace Violet (CTV) dilution. T cells were labeled with the cell penetrating dye CTV and incubated with target cells (M14Luc) and titrated with BsAb for 96 hrs. The frequency of cells fluorescing with less remaining CTV than an unstimulated control was considered to have divided at least once. As such, proliferation was the greatest for the 2+2 and reduced for all other IgG-[L]-scFv variants (right). No activation or proliferation was observed with any construct in the absence of tumor cells (data not shown) indicating that there is minimal activation without target antigen. These results demonstrate that a cis interaction is considerably more potent than a trans interaction (1+1C vs 1+1T) and furthermore that two cis interactions are more potent than one (2+2 vs 1+1C or 1+2 or 2+1) (two cis interactions are only possible in a dual bivalent approach, such as the 2+2 IgG-[L]-scFv).

[0329] These results demonstrate that the HDTVS antibodies disclosed herein are useful in methods for treating a disease or condition, such as cancer.

Example 8: Modifications of the 2+2 IgG-[L]-scFv and their Relative In Vivo Tumor Clearance

[0330] FIG. **7** describes the in vivo anti-tumor activity of each IgG-[L]-scFv variant in two different tumor models. As illustrated in FIG. **7**, the in vivo anti-tumor activity of each variant largely correlated with in vitro cytotoxicity. In the xenograft model (right) the strongest anti-tumor activity was imparted by the 2+2 BsAb. Surprisingly, the 2+1 was very similar, with only a slight difference in tumor recurrence (5/5 CR for both). As with the cytotoxicity data, the next most effective were the 1+1C and 1+2, validating both in vitro findings that the cis orientation is superior to the trans and the 2+1 was superior to the 1+2. All other variants (1+1T, IgG-Het, control BsAb) failed to show any effect on tumor growth. In the more aggressive syngeneic model using EL.4 tumors (as done in FIG. **1**), no IgG-[L]-scFv variant aside from the 2+2 showed an anti-tumor effect. As opposed to the xenograft model where activated T-cells are directly administered to the mouse, the syngeneic model requires activation in situ, suggesting that the in vitro cell activation differences may manifest in vivo leading to diminished capacity to shrink tumors. Taken together, these results suggest that the optimal BsAb platform is capable of strong cell activation in the presence of antigen, and that bivalency toward both cell populations, target cells and effector cells, is critical. In addition, these results confirm the importance of two cis-interactions in a bispecific antibody (2+2) over all single cis-interacting variants (2+1, 1+1C, 1+2) or non-cis interacting variants (1+1T, 1+1H).

[0331] These results demonstrate that the HDTVS antibodies disclosed herein are useful in methods for treating a disease or condition, such as cancer.

Example 9: 2+2 IgG-[L]-scFv is Superior to Other Bivalent Antibody Designs

[0332] FIG. **8** shows cytotoxicity and conjugate formation activity from 3 additional 2+2 designs, thus demonstrating the overall superiority of the IgG-[L]-scFv format. The 2+2 IgG-[L]-scFv format was more demonstrably more potent than other conventional 2+2 formats. The IgG-chemical conjugate (Yankelevich et al., *Pediatr Blood Cancer* 59:1198-1205 (2012)) the IgG-[H]-scFv (with scFv attached at the C-terminus of the HC instead of the LC of the IgG; Coloma & Morrison, *Nat Biotechnol* 15:159-163 (1997)) and the BITE-Fc, all failed to kill cells as potently in vitro, compared with the IgG-[L]-scFv design. The poor cytotoxic effects were observed despite apparently improved conjugate formation activity (bottom left) and cell binding activity (bottom right). These results demonstrate that the structural features of the IgG-[L]-scFv format (unique flexibility, orientations and arrangements of the four antigen binding domains) may be correlated with effects on T-cell recruitment, activation and cytotoxicity. FIGS. **12***a*-**12***c* show the in vivo anti-tumor activity from two additional 2+2 designs, thus confirming the overall superiority of the IgG-[L]-scFv format (2+2). Using an in vivo T-cell arming model, only the IgG-[L]-scFv format (2+2) of the present technology was able to inhibit tumor growth. Strikingly, despite the dual bivalency of the dimeric BiTE-Fc and the IgG-[H]-scFv,

both failed to display any anti-tumor activity compared to the control BsAb. These results confirm the in vitro findings, that the superiority of the IgG-[L]-scFv design is not strictly due to decreased distance between binding domains, but instead suggests that the potency of the IgG-[L]-scFv is not simply a function of minimization of intermembrane distance. Rather, the exceptional in vitro and in vivo potency of the IgG-[L]-scFv may be attributed at least in part to the properties of cis-configured Fab and scFv domains, spaced apart with a single Ig domain (CL), such as stiffness or flexibility.

[0333] These results demonstrate that the HDTVS antibodies disclosed herein are useful in methods for treating a disease or condition, such as cancer.

Example 10: 2+2 IgG-[L]-scFv and Subset of Variants Against Alternative Antigens

[0334] FIG. **9** describes some of the differences in activity observed with different tumor antigens. As illustrated in FIG. **9**, the IgG-[L]-scFv platform does depend in part on the tumor antigen. When targeted to CD33 (top panels) a similar pattern of cell binding and cytotoxicity was found. CD33(+) MOLM13-fluc cells were assayed as described in FIG. **4** (left). As with GD2, reduction in valency (1+1T, 1+1C, or 1+2) significantly decreased binding activity. In terms of cytotoxicity, the Cis/Trans orientation appeared to play less of a role (both 1+1T and 1+C are most inferior, and equivalent to IgG-Het), and therefore the difference between the 2+1 and 1+2 was diminished. The lack of cis/trans difference may also explain the overall worse EC_{50} against CD33(+) MOLM-13fluc as compared to GD2(+) M14Luc or IMR32Luc. When the tumor antigen was changed to HER2 (lower panels), and the antigen binding domains possessed significantly higher binding affinity, a different pattern was observed. 2+2 and 1+2 variants appeared identical, with similar tumor binding levels despite the monovalency. This suggests that with sufficiently high affinities, the second tumor binding domain is dispensable, as predicated in the Hi1+1+2 HDTVS design.

[0335] These results demonstrate that the HDTVS antibodies disclosed herein are useful in methods for treating a disease or condition, such as cancer.

Example 11: Hi1+1+2 and Lo1+1+2 Proof of Concept Studies

[0336] As depicted in FIG. **10***a* (left side), the 2(HER2)+2(CD3) functions similarly to the 1(HER2)+2(CD3), where only one Fab domain binds the tumor and the second Fab recognizes an irrelevant antigen, due to the very high affinity interaction between HER2 and the anti-HER2 Fab used (Herceptin). In both FACS binding (top) and an in vitro cytotoxicity assay (bottom) with U2OS cells, the 2(HER2)+2(CD3) and the 1(HER2)+2(CD3) were indistinguishable, highlighting the possibility of using the second Fab arm to target a separate antigen. Conversely, the Lo1(GD2)+1(GD2)+2(CD3) (right side), shows the utility of two separate tumor antigen specificities when binding affinities are sufficiently low. Here the 2(GD2)+2(CD3), the 1(GD2)+2(CD3) and Lo1(GD2)+1(GD2)+2(CD3) showed major differences that are explained by the differences in valency between constructs. In both FACS binding (top) and in vitro cytotoxicity (bottom) with U2OS cells, the 2(GD2)+2(CD3) displayed superior activity over a 1(GD2)+2(CD3) format having an irrelevant second specificity (thus limiting binding to monovalency). However, adding a second relevant Fab binding specificity (e.g. HER2) in Lo1(GD2)+1(HER2)+2(CD3) was able to rescue this defect and even improve binding and killing. These results highlight the utility of targeting two separate antigens on the same cell when the Fab affinity for each individual antigen is sufficiently low (e.g., 100 pM to 100 nM K_D). Additionally, the approximately 100-fold difference in EC_{50} between the Lo1(GD2)+1(HER2)+2(CD3) and 1(GD2)+2(CD3) validates the improved therapeutic index between monovalent and bivalent binding of a Lo1(GD2)+1(HER2)+2(CD3) construct. Had the second specificity (i.e. HER2) of the Lo1+1+2 (GD2) been irrelevant (no binding to tumor or T cells), it would have functioned as the 1(GD2)+2(CD3) with 100-fold less activity. This is in contrast to the 2+2 which would not be able to distinguish a dual-antigen positive tumor from a GD2(+) normal tissue (such as peripheral nerves).

[0337] As shown in FIG. **10***b*, when these two sets of constructs were presented to tumor cells expressing high levels of only one antigen (HER2 and GD2, left and right sides respectively), the same patterns were observed. With the 2(HER2)+2(CD3) and 1(HER2)+2(CD3), similar FACS binding and cytotoxicity were observed against the HCC1954 cell line which shows high expression of HER2 (+). However, stronger binding and cytotoxicity was observed with the 2(GD2)+2(CD3) compared to the 1(GD2)+2(CD3) and a Lo1(GD2)+1(HER2)+2(CD3) having an irrelevant second specificity (second Fab domain did not recognize the tumor cell line IMR32Luc).

[0338] Taken together, with a sufficiently high effective affinity interaction a 1+2 IgG-[L]-scFv functions identically to a 2+2, suggesting the Hi1+1+2 can be used to target two separate antigens instead of just one. However, with a sufficiently low effective affinity interaction, a Lo1+1+2 can provide an improved therapeutic index to distinguish between single antigen positive normal tissue and double antigen positive tumor cells.

[0339] These results demonstrate that the HDTVS antibodies disclosed herein are useful in methods for treating a disease or condition, such as cancer.

Example 12: Binding Affinity and Cytotoxic Selectivity of the Low Affinity 1+1+2 Format Antibodies of the Present Technology

[0340] The binding affinity of L1CAM/GD2 1+1+2 Lo, a heterodimeric 1+1+2Lo format antibody, which can bind ganglioside GD2 and adhesion protein L1CAM simultaneously, was compared with homodimeric formats against GD2 and L1CAM. Neuroblastoma cells (IMR32) were incubated with each antibody for 30 minutes at 4° C., washed and incubated with a fluorescent anti-human secondary antibody. After the final wash, the cells were analyzed using flow cytometry. As shown in FIG. **13**, the binding of the low affinity 1+1+2 HDTVS antibody was stronger than that of the anti-L1CAM homodimeric antibody, but weaker than the anti-GD2 homodimeric antibody, thus showing improved targeting specificity for tumors expressing both GD2 and L1CAM.

[0341] The combined binding effect of GD2/B7H3 1+1+2 Lo, a heterodimeric 1+1+2Lo format antibody, which can bind both GD2 and B7H3 simultaneously was also compared with the homodimeric format antibodies against GD2 and B7H3, and monovalent control antibodies against GD2

or B7H3. Osteosarcoma cells (U2OS) were incubated with each antibody for 30 minutes at 4° C., washed and incubated with a fluorescent anti-human secondary antibody. After the final wash, the cells were analyzed using flow cytometry. As shown in FIG. **15**, the binding of the low affinity 1+1+2 heterodimer antibody was similar to the anti-B7H3 homodimeric antibody, but weaker than the anti-GD2 homodimeric antibody. Importantly, the GD2/B7H3 1+1+2 Lo HDTVS antibody also shows improved binding over monovalent control antibodies, thus demonstrating cooperative binding of the heterodimeric GD2/B7H3 1+1+2 Lo antibody.

[0342] To assess the cytotoxic selectivity of the low affinity 1+1+2Lo format antibodies of the present technology, HER2/GD2 1+1+2 Lo, a heterodimeric 1+1+2Lo format antibody, which can bind both GD2 and HER2 simultaneously, was studied. In this format, a low affinity HER2 sequence was used. Homodimeric formats against GD2 and HER2, and monovalent control antibodies against GD2 or HER2 were included for reference. Osteosarcoma cells (U2OS) were first incubated with ^{51}Cr for one hour. After the incubation, the ^{51}Cr labeled target cells were mixed with serial dilutions of the antibodies and activated human T-cells for four hours at 37° C. After four hours, supernatant was harvested and analyzed on a gamma counter to quantify the released ^{51}Cr. As shown in FIG. **16**, the low affinity 1+1+2 heterodimer antibody killed U2OS cells as effectively as the anti-GD2 and anti-HER2 homodimeric antibodies and showed clear superiority over the monovalent control formats. Therefore, the 1+1+2Lo design exhibited 10-100-fold lower cytotoxic potency in cells expressing each individual antigen compared to target cells expressing both antigens simultaneously. A homodimeric design for either GD2 or HER2 would not be expected to exhibit such selectivity.

[0343] These results demonstrate the selective cytotoxicity could be attained with the 1+1+2Lo design by targeting cells expressing each individual antigen with 10-100-fold lower cytotoxic potency than targets expressing both antigens simultaneously.

[0344] Accordingly, the 1+1+2Lo format antibodies of the present technology are useful in methods for treating a disease or condition, such as cancer.

Example 13: Binding Affinity and Cytotoxic Dual Specificity of the 1+1+2Hi Format Antibodies of the Present Technology

[0345] To assess the binding affinity of the heterodimeric 1+1+2Hi format antibodies of the present technology, the combined binding effect of HER2/EGFR 1+1+2Hi, a heterodimeric 1+1+2Hi format antibody, which can bind both HER2 and EGFR, either simultaneously or separately, was analyzed. Homodimeric formats against HER2 and EGFR were included for reference. Desmoplastic Small Cell Round Tumor cells (JN-DSRCT1) were incubated with each antibody for 30 minutes at 4° C., washed and incubated with a fluorescent anti-human secondary antibody. As shown in FIG. **14**, the binding of the high affinity 1+1+2 heterodimer antibody was stronger than that of either anti-HER2 or anti-EGFR homodimeric antibodies, while maintaining specificity for both antigens, thus demonstrating cooperative binding.

[0346] HER2/GPA33 1+1+2 Hi, a heterodimeric 1+1+2Hi format antibody, which can bind both GPA33 and HER2 either simultaneously or separately, was compared with the homodimeric format antibodies against GPA33 and HER2, and monovalent control antibodies against GPA33 or HER2. To compare the combined binding effect, colon cancer cells (Colo205) were incubated with each antibody for 30 minutes at 4° C., washed and incubated with a fluorescent anti-human secondary antibody. After the final wash, the cells were analyzed using flow cytometry. HER2/GPA33 1+1+2 Hi antibody bound both HER2 and GPA33 on Colo205 cells, either simultaneously or separately (FIG. **17***b*). As shown in FIG. **17***b*, the binding affinity of the 1+1+2Hi heterodimer antibody was stronger than either anti-HER2 or anti-GPA33 homodimeric and monovalent control antibodies, while maintaining specificity for both antigens, thus demonstrating cooperative binding.

[0347] To evaluate the cytotoxic specificity of the HER2/GPA33 1+1+2Hi format antibody, colon cancer cells (Colo205) were first incubated with ^{51}Cr for one hour. After the incubation, the ^{51}Cr labeled target cells were mixed with serial dilutions of the indicated antibody and activated human T-cells for four hours at 37° C. After four hours, the supernatant was harvested and read on a gamma counter to quantify the released ^{51}Cr. Cytotoxicity was measured as the % of released ^{51}Cr from maximum release. As shown in FIG. **17***a*, the high affinity 1+1+2 heterodimer antibody killed Colo205 cells as effectively as the anti-GPA33 homodimeric antibody, but with greater potency than the anti-HER2 homodimeric antibody and monovalent control antibodies. These results demonstrate functional cooperativity between the HER2 and GPA33 antigen binding domains, and illustrate that the dual specificity of a 1+1+2Hi format does not significantly compromise its cytotoxicity against either antigen individually.

[0348] Accordingly, the 1+1+2Hi format antibodies of the present technology are useful in methods for treating a disease or condition, such as cancer.

Example 14: Combined Binding Effects and Cytokine Release Induced by the 2+1+1 Format Antibodies of the Present Technology

[0349] To evaluate the combined binding effects of the heterodimeric 2+1+1 format antibodies of the present technology, several heterodimeric 2+1+1 format antibodies were compared with their corresponding homodimeric format antibodies and monovalent control antibodies. For example, CD3/CD4 2+1+1, a heterodimeric 2+1+1 format antibody that can bind both CD3 and CD4 simultaneously was compared with its corresponding bivalent format antibodies against CD3 and CD4, and a monomeric CD3 binder (2+1). For this binding assay, active human T cells were incubated with each antibody for 30 minutes at 4° C., washed and incubated with a fluorescent anti-human secondary antibody. After the final wash, the cells were analyzed using flow cytometry. As shown in FIG. **19**, the binding of CD3/CD4 2+1+1 antibodies showed enhanced binding compared to the bivalent CD4 antibody and monomeric CD3 binder (2+1), thus demonstrating cooperative binding.

[0350] Similarly, binding of CD3/PD-1 2+1+1, a heterodimeric 2+1+1 format antibody that can bind both CD3 and PD-1 simultaneously, was compared with homodimeric anti-PD-1 and anti-CD3 antibodies, and with an anti-CD3 monomeric (2+1) binder. For this binding assay active human T cells were incubated with each antibody for 30 minutes at 4° C., washed and incubated with a fluorescent anti-human secondary antibody. After the final wash, the cells were analyzed using flow cytometry. As shown in FIG. **20**, the

2+1+1 heterodimer antibody bound cells better than either anti-PD-1 homodimeric antibody or anti-CD3 monomeric (2+1) binder, thus demonstrating cooperative binding. Collectively, these data demonstrate that a heterodimeric 2+1+1 format antibody of the present technology binds its target better than the corresponding weaker-binding homodimeric antibody and its corresponding monomeric (2+1) binder, thus demonstrating cooperative binding.

[0351] Next, cytokine release induced by CD3/CD28 2+1+1, a heterodimeric 2+1+1 format antibody, was analyzed. The homodimeric format antibodies against CD3 and CD28 were included for reference. Naïve human T-cells and melanoma tumor cells (M14) were co-cultured along with the indicated BsAb for 20 hours. Culture supernatants were harvested following the incubation and analyzed for secreted cytokine IL-2 by FACS. Data were normalized to T-cell cytokine release after 20 hours without target cells or antibody. As shown in FIG. **18**, the CD3/CD28 2+1+1 antibody showed more potent cytokine release activity compared to either CD3 or CD28 engagement alone, illustrating cooperative activity from dual CD3/CD28 engagement. These results demonstrate the utility of a heterodimeric 2+1+1 design that can bind both CD3 and CD28 on T-cells.

[0352] Accordingly, the 2+1+1 format antibodies of the present technology are useful in methods for treating a disease or condition, such as cancer.

Example 15: Comparison of the IgG-L-scFv Format of the Present Technology with BiTE-Fc and IgG-H-scFv Formats

[0353] The IgG-L-scFv design was next compared with two other common dual bivalent design strategies: the BiTE-Fc and the IgG-H-scFv formats. First, to compare cytokine release induced by IgG-L-scFv design compared to BiTE-Fc and the IgG-H-scFv, naïve T-cells and melanoma tumor cells (M14) were co-cultured along with each BsAb for 20 hours. Culture supernatants were harvested and analyzed for secreted cytokine IL-2. Data were normalized to T-cell cytokine release after 20 hours without target cells or antibody. As shown in FIG. **21***a*, the IgG-L-scFv design (2+2) exhibited unusually potent T-cell functional activity compared to other dual bivalent T-cell bispecific antibody formats.

[0354] To compare binding intensity, T-cells and melanoma tumor cells (M14) were separately incubated with each antibody for 30 minutes at 4° C., washed and incubated with a fluorescent anti-human secondary antibody. After the final wash, the cells were analyzed using flow cytometry. As shown in FIG. **21***b* (upper panel), IgG-L-scFv design showed unusually weak T-cell binding activity compared to other dual bivalent T-cell bispecific antibody formats. In contrast to their GD2 binding activity (FIG. **21***b* (middle panel)), each BsAb demonstrated quite different T-cell binding activities. These data demonstrated how the IgG-L-scFv design is uniquely different than other dual-bivalent designs, with each scFv showing incomplete bivalent binding. Although the inclusion of two scFv domains in the IgG-L-scFv did result in an improvement over monovalent designs, it still did not compare to the binding activity of the 2+2 IgG-H-scFv or 2+2 BiTE-Fc designs, illustrating the sterically hindered binding of this format.

[0355] The effect of the observed binding and cytokine release profiles on the in vivo antitumor activity was explored next. Immunodeficient mice (Balb/c IL-2Rgc−/−, Rag2−/−) were implanted with neuroblastoma cells (IMR32) subcutaneously and treated with intravenous activated T-cells and antibody (2-times per week). Tumors sizes were measured by caliper. As shown in FIG. **21***c*, the IgG-L-scFv design antibodies inhibited tumor growth. In comparison, the IgG-H-scFv and BiTE-Fc design antibodies showed a borderline in vivo effect. Therefore, in contrast to the IgG-H-scFv (2+2HC) and the BiTE-Fc (2+2B) designs, the IgG-L-scFv format (2+2) demonstrated significant cytokine IL-2 responses in vitro (FIG. **21***a*), which correlated with stronger in vivo activity (FIG. **21***c*).

[0356] Collectively, these data demonstrate the in vivo superiority of the IgG-L-scFv format antibodies in that only the IgG-L-scFv format antibodies were capable of inhibiting tumor growth in animals in contrast to other dual bivalent designs.

[0357] These results demonstrate that the HDTVS antibodies disclosed herein are useful in methods for treating a disease or condition, such as cancer.

Example 16: Importance of Cis-Oriented Binding Domains with Respect to In Vitro Properties of an Anti-IgG-[L]-scFv Antibody

[0358] To further understand the in vitro properties of antibodies of various designs, a anti-CD33 IgG-[L]-scFv panel was created, and the in vitro cytotoxicity EC_{50}, fold-difference in EC_{50}, antigen valency, heterodimer design and protein purity were examined. FIG. **22** summarizes the data. Fold change was based on the EC_{50} of 2+2. Purity was calculated as the fraction of protein at correct elution time out of the total protein by area under the curve of the SEC-HPLC chromatogram. For the cytotoxicity assays, CD33-transfected cells (Nalm6) were first incubated with ^{51}Cr for one hour. Afterwards, ^{51}Cr labeled target cells were mixed with serial titrations of the indicated antibody and activated human T-cells for four hours at 37° C. The supernatant was harvested and analyzed on a gamma counter to quantify the released ^{51}Cr. Cytotoxicity was measured as the % of released ^{51}Cr from maximum release. These results shown in FIG. **22** confirm the relative importance of cis-oriented binding domains in an additional antigen system (CD33) which is much more membrane distal than GD2 (see FIG. **5**).

[0359] These results demonstrate that the HDTVS antibodies disclosed herein are useful in methods for treating a disease or condition, such as cancer.

EQUIVALENTS

[0360] The present technology is not to be limited in terms of the particular embodiments described in this application, which are intended as single illustrations of individual aspects of the present technology. Many modifications and variations of this present technology can be made without departing from its spirit and scope, as will be apparent to those skilled in the art. Functionally equivalent methods and apparatuses within the scope of the present technology, in addition to those enumerated herein, will be apparent to those skilled in the art from the foregoing descriptions. Such modifications and variations are intended to fall within the scope of the present technology. It is to be understood that this present technology is not limited to particular methods, reagents, compounds compositions or biological systems, which can, of course, vary. It is also to be understood that the

terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

[0361] In addition, where features or aspects of the disclosure are described in terms of Markush groups, those skilled in the art will recognize that the disclosure is also thereby described in terms of any individual member or subgroup of members of the Markush group.

[0362] As will be understood by one skilled in the art, for any and all purposes, particularly in terms of providing a written description, all ranges disclosed herein also encompass any and all possible subranges and combinations of subranges thereof. Any listed range can be easily recognized as sufficiently describing and enabling the same range being broken down into at least equal halves, thirds, quarters, fifths, tenths, etc. As a non-limiting example, each range discussed herein can be readily broken down into a lower third, middle third and upper third, etc. As will also be understood by one skilled in the art all language such as "up to," "at least," "greater than," "less than," and the like, include the number recited and refer to ranges which can be subsequently broken down into subranges as discussed above. Finally, as will be understood by one skilled in the art, a range includes each individual member. Thus, for example, a group having 1-3 cells refers to groups having 1, 2, or 3 cells. Similarly, a group having 1-5 cells refers to groups having 1, 2, 3, 4, or 5 cells, and so forth.

[0363] All patents, patent applications, provisional applications, and publications referred to or cited herein are incorporated by reference in their entirety, including all figures and tables, to the extent they are not inconsistent with the explicit teachings of this specification.

SEQUENCE LISTING

The patent application contains a lengthy "Sequence Listing" section. A copy of the "Sequence Listing" is available in electronic form from the USPTO web site (https://seqdata.uspto.gov/?pageRequest=docDetail&DocID=US20220098329A1). An electronic copy of the "Sequence Listing" will also be available from the USPTO upon request and payment of the fee set forth in 37 CFR 1.19(b)(3).

1. A heterodimeric multispecific antibody comprising a first polypeptide chain, a second polypeptide chain, a third polypeptide chain and a fourth polypeptide chain, wherein the first and second polypeptide chains are covalently bonded to one another, the second and third polypeptide chains are covalently bonded to one another, and the third and fourth polypeptide chain, and wherein:

a. the first polypeptide chain comprises in the N-terminal to C-terminal direction:
   i. a light chain variable domain of a first immunoglobulin (VL-1) that is capable of specifically binding to a first epitope;
   ii. a light chain constant domain of the first immunoglobulin (CL-1);
   iii. a flexible peptide linker comprising the amino acid sequence $(GGGGS)_3$ (SEQ ID NO: 2506); and
   iv. a light chain variable domain of a second immunoglobulin (VL-2) that is linked to a complementary heavy chain variable domain of the second immunoglobulin (VH-2), or a heavy chain variable domain of a second immunoglobulin (VH-2) that is linked to a complementary light chain variable domain of the second immunoglobulin (VL-2), wherein VL-2 and VH-2 are capable of specifically binding to a second epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ (SEQ ID NO: 2507) to form a single-chain variable fragment;

b. the second polypeptide comprises in the N-terminal to C-terminal direction:
   i. a heavy chain variable domain of the first immunoglobulin (VH-1) that is capable of specifically binding to the first epitope;
   ii. a first CH1 domain of the first immunoglobulin (CH1-1); and
   iii. a first heterodimerization domain of the first immunoglobulin, wherein the first heterodimerization domain is incapable of forming a stable homodimer with another first heterodimerization domain;

c. the third polypeptide comprises in the N-terminal to C-terminal direction:
   i. a heavy chain variable domain of a third immunoglobulin (VH-3) that is capable of specifically binding to a third epitope;
   ii. a second CH1 domain of the third immunoglobulin (CH1-3); and
   iii. a second heterodimerization domain of the third immunoglobulin, wherein the second heterodimerization domain comprises an amino acid sequence or a nucleic acid sequence that is distinct from the first heterodimerization domain of the first immunoglobulin, wherein the second heterodimerization domain is incapable of forming a stable homodimer with another second heterodimerization domain, and wherein the second heterodimerization domain of the third immunoglobulin is configured to form a heterodimer with the first heterodimerization domain of the first immunoglobulin;

d. the fourth polypeptide comprises in the N-terminal to C-terminal direction:
   i. a light chain variable domain of the third immunoglobulin (VL-3) that is capable of specifically binding to the third epitope;
   ii. a light chain constant domain of the third immunoglobulin (CL-3);
   iii. a flexible peptide linker comprising the amino acid sequence $(GGGGS)_3$ (SEQ ID NO: 2506); and
   iv. a light chain variable domain of a fourth immunoglobulin (VL-4) that is linked to a complementary heavy chain variable domain of the fourth immuno-

globulin (VH-4), or a heavy chain variable domain of a fourth immunoglobulin (VH-4) that is linked to a complementary light chain variable domain of the fourth immunoglobulin (VL-4), wherein VL-4 and VH-4 are capable of specifically binding to the second epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ (SEQ ID NO: 2507) to form a single-chain variable fragment, and

wherein each of VL-1 and VL-3 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_L amino acid sequence selected from any one of SEQ ID NOs: 1, 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 105, 113, 121, 129, 145, 153, 161, 169, 177, 193, 201, 233, 241, 257, 273, 281, 289, 297, 305, 313, 321, 329, 337, 345, 353, 361, 369, 377, 385, 393, 401, 409, 417, 425, 433, 441, 449, 457, 465, 481, 489, 497, 521, 529, 537, 545, 553, 561, 609, 617, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 777, 785, 793, 801, 809, 817, 825, 833, 841, 849, 857, 865, 873, 881, 889, 945, 953, 961, 977, 985, 993, 1001, 1009, 1017, 1025, 1033, 1041, 1049, 1065, 1073, 1081, 1089, 1097, 1105, 1113, 1121, 1129, 1137, 1145, 1153, 1161, 1169, 1177, 1185, 1193, 1201, 1209, 1217, 1225, 1233, 1241, 1249, 1257, 1265, 1273, 1281, 1289, 1297, 1305, 1313, 1321, 1329, 1337, 1345, 1353, 1361, 1369, 1377, 1385, 1393, 1401, 1409, 1417, 1425, 1433, 1441, 1449, 1457, 1465, 1473, 1481, 1489, 1497, 1505, 1513, 1521, 1529, 1545, 1553, 1561, 1569, 1577, 1585, 1593, 1601, 1609, 1617, 1625, 1633, 1649, 1657, 1673, 1681, 1689, 1697, 1705, 1713, 1721, 1729, 1737, 1745, 1753, 1761, 1769, 1777, 1785, 1793, 1801, 1809, 1817, 1833, 1841, 1849, 1857, 1865, 1873, 1881, 1889, 1913, 1937, 1945, 1953, 1961, 1969, 1977, 1985, 1993, 2001, 2009, 2017, 2025, 2033, 2041, 2049, 2057, 2065, 2073, 2081, 2089, 2097, 2105, 2113, 2121, 2129, 2137, 2145, 2153, 2161, 2169, 2177, 2185, 2193, 2201, 2209, 2217, 2225, 2233, 2241, 2249, 2257, 2265, 2273, 2281, 2297, 2305, 2313, 2321, 2329, 2337 and 2345; and/or

wherein each of VH-1 and VH-3 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_H amino acid sequence selected from any one of SEQ ID NOs: 5, 13, 21, 29, 37, 45, 53, 61, 69, 77, 85, 93, 101, 109, 117, 125, 133, 149, 157, 165, 173, 181, 197, 205, 237, 245, 261, 277, 285, 293, 301, 309, 317, 325, 333, 341, 349, 357, 365, 373, 381, 389, 397, 405, 413, 421, 429, 437, 445, 453, 461, 469, 485, 493, 501, 525, 533, 541, 549, 557, 565, 613, 621, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 781, 789, 797, 805, 813, 821, 829, 837, 845, 853, 861, 869, 877, 885, 893, 949, 957, 965, 981, 989, 997, 1005, 1013, 1021, 1029, 1037, 1045, 1053, 1069, 1077, 1085, 1093, 1101, 1109, 1117, 1125, 1133, 1141, 1149, 1157, 1165, 1173, 1181, 1189, 1197, 1205, 1213, 1221, 1229, 1237, 1245, 1253, 1261, 1269, 1277, 1285, 1293, 1301, 1309, 1317, 1325, 1333, 1341, 1349, 1357, 1365, 1373, 1381, 1389, 1397, 1405, 1413, 1421, 1429, 1437, 1445, 1453, 1461, 1469, 1477, 1485, 1493, 1501, 1509, 1517, 1525, 1533, 1549, 1557, 1565, 1573, 1581, 1589, 1597, 1605, 1613, 1621, 1629, 1637, 1653, 1661, 1677, 1685, 1693, 1701, 1709, 1717, 1725, 1733, 1741, 1749, 1757, 1765, 1773, 1781, 1789, 1797, 1805, 1813, 1821, 1837, 1845, 1853, 1861, 1869, 1877, 1885, 1893, 1917, 1941, 1949, 1957, 1965, 1973, 1981, 1989, 1997, 2005, 2013, 2021, 2029, 2037, 2045, 2053, 2061, 2069, 2077, 2085, 2093, 2101, 2109, 2117, 2125, 2133, 2141, 2149, 2157, 2165, 2173, 2181, 2189, 2197, 2205, 2213, 2221, 2229, 2237, 2245, 2253, 2261, 2269, 2277, 2285, 2301, 2309, 2317, 2325, 2333, 2341, and 2349.

2. A heterodimeric multispecific antibody comprising a first polypeptide chain, a second polypeptide chain, a third polypeptide chain and a fourth polypeptide chain, wherein the first and second polypeptide chains are covalently bonded to one another, the second and third polypeptide chains are covalently bonded to one another, and the third and fourth polypeptide chain, and wherein:

a. the first polypeptide chain comprises in the N-terminal to C-terminal direction:

i. a light chain variable domain of a first immunoglobulin (VL-1) that is capable of specifically binding to a first epitope;

ii. a light chain constant domain of the first immunoglobulin (CL-1);

iii. a flexible peptide linker comprising the amino acid sequence $(GGGGS)_3$ (SEQ ID NO: 2506); and

iv. a light chain variable domain of a second immunoglobulin (VL-2) that is linked to a complementary heavy chain variable domain of the second immunoglobulin (VH-2), or a heavy chain variable domain of a second immunoglobulin (VH-2) that is linked to a complementary light chain variable domain of the second immunoglobulin (VL-2), wherein the VL-2 and VH-2 are capable of specifically binding to a second epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ (SEQ ID NO: 2507) to form a single-chain variable fragment;

b. the second polypeptide comprises in the N-terminal to C-terminal direction:

i. a heavy chain variable domain of the first immunoglobulin (VH-1) that is capable of specifically binding to the first epitope;

ii. a first CH1 domain of the first immunoglobulin (CH1-1); and

iii. a first heterodimerization domain of the first immunoglobulin, wherein the first heterodimerization domain is incapable of forming a stable homodimer with another first heterodimerization domain;

c. the third polypeptide comprises in the N-terminal to C-terminal direction:

i. a heavy chain variable domain of a third immunoglobulin (VH-3) that is capable of specifically binding to the first epitope;

ii. a second CH1 domain of the third immunoglobulin (CH1-3); and

iii. a second heterodimerization domain of the third immunoglobulin, wherein the second heterodimerization domain comprises an amino acid sequence or a nucleic acid sequence that is distinct from the first heterodimerization domain of the first immunoglobulin, wherein the second heterodimerization domain is incapable of forming a stable homodimer with another second heterodimerization domain, and wherein the second heterodimerization domain of the third immunoglobulin is configured to form a heterodimer with the first heterodimerization domain of the first immunoglobulin;

d. the fourth polypeptide comprises in the N-terminal to C-terminal direction:
   i. a light chain variable domain of the third immunoglobulin (VL-3) that is capable of specifically binding to the first epitope;
   ii. a light chain constant domain of the third immunoglobulin (CL-3);
   iii. a flexible peptide linker comprising the amino acid sequence $(GGGGS)_3$ (SEQ ID NO: 2506); and
   iv. a light chain variable domain of a fourth immunoglobulin (VL-4) that is linked to a complementary heavy chain variable domain of the fourth immunoglobulin (VH-4), or a heavy chain variable domain of a fourth immunoglobulin (VH-4) that is linked to a complementary light chain variable domain of the fourth immunoglobulin (VL-4), wherein the VL-4 and VH-4 are capable of specifically binding to a third epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ (SEQ ID NO: 2507) to form a single-chain variable fragment, and

wherein each of VL-2 and VL-4 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_L amino acid sequence selected from any one of SEQ ID NOs: 17, 25, 33, 41, 121, 137, 169, 177, 185, 193, 201, 209, 217, 225, 233, 241, 249, 257, 265, 321, 329, 337, 393, 401, 409, 473, 481, 489, 497, 505, 513, 545, 553, 561, 569, 577, 585, 593, 601, 625, 633, 641, 649, 657, 665, 673, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 785, 793, 801, 809, 817, 849, 857, 865, 873, 881, 889, 897, 905, 913, 921, 929, 937, 945, 969, 977, 1009, 1057, 1537, 1569, 1601, 1641, 1665, 1825, 1865, 1897, 1905, 1913, 1921, 1929, 2265, 2281 2289, 2329, and 2345; and/or

wherein each of V-2 and VH-4 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_H amino acid sequence selected from any one of SEQ ID NOs: 21, 29, 37, 45, 125, 141, 173, 181, 189, 197, 205, 213, 221, 229, 237, 245, 253, 261, 269, 325, 333, 341, 397, 405, 413, 477, 485, 493, 501, 509, 517, 549, 557, 565, 573, 581, 589, 597, 605, 629, 637, 645, 653, 661, 669, 677, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 789, 797, 805, 813, 821, 853, 861, 869, 877, 885, 893, 901, 909, 917, 925, 933, 941, 949, 973, 981, 1013, 1061, 1541, 1573, 1605, 1645, 1669, 1829, 1869, 1901, 1909, 1917, 1925, 1933, 2269, 2285, 2293, 2333, and 2349.

3. A heterodimeric multispecific antibody comprising a first polypeptide chain, a second polypeptide chain, a third polypeptide chain and a fourth polypeptide chain, wherein the first and second polypeptide chains are covalently bonded to one another, the second and third polypeptide chains are covalently bonded to one another, and the third and fourth polypeptide chain, and wherein:

a. the first polypeptide chain comprises in the N-terminal to C-terminal direction:
   i. a light chain variable domain of a first immunoglobulin (VL-1) that is capable of specifically binding to a first epitope;
   ii. a light chain constant domain of the first immunoglobulin (CL-1);
   iii. a flexible peptide linker comprising the amino acid sequence $(GGGGS)_3$ (SEQ ID NO: 2506); and
   iv. a light chain variable domain of a second immunoglobulin (VL-2) that is linked to a complementary heavy chain variable domain of the second immunoglobulin (VH-2), or a heavy chain variable domain of a second immunoglobulin (VH-2) that is linked to a complementary light chain variable domain of the second immunoglobulin (VL-2), wherein VL-2 and VH-2 are capable of specifically binding to a second epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ (SEQ ID NO: 2507) to form a single-chain variable fragment;
b. the second polypeptide comprises in the N-terminal to C-terminal direction:
   i. a heavy chain variable domain of the first immunoglobulin (VH-1) that is capable of specifically binding to the first epitope;
   ii. a first CH1 domain of the first immunoglobulin (CH1-1); and
   iii. a first heterodimerization domain of the first immunoglobulin, wherein the first heterodimerization domain is incapable of forming a stable homodimer with another first heterodimerization domain;
c. the third polypeptide comprises in the N-terminal to C-terminal direction:
   i. a heavy chain variable domain of a third immunoglobulin (VH-3) that is capable of specifically binding to a third epitope;
   ii. a second CH1 domain of the third immunoglobulin (CH1-3); and
   iii. a second heterodimerization domain of the third immunoglobulin, wherein the second heterodimerization domain comprises an amino acid sequence or a nucleic acid sequence that is distinct from the first heterodimerization domain of the first immunoglobulin, wherein the second heterodimerization domain is incapable of forming a stable homodimer with another second heterodimerization domain, and wherein the second heterodimerization domain of the third immunoglobulin is configured to form a heterodimer with the first heterodimerization domain of the first immunoglobulin;
d. the fourth polypeptide comprises in the N-terminal to C-terminal direction:
   i. a light chain variable domain of the third immunoglobulin (VL-3) that is capable of specifically binding to the third epitope;
   ii. a light chain constant domain of the third immunoglobulin (CL-3);
   iii. a flexible peptide linker comprising the amino acid sequence $(GGGGS)_3$ (SEQ ID NO: 2506); and
   iv. a light chain variable domain of a fourth immunoglobulin (VL-4) that is linked to a complementary heavy chain variable domain of the fourth immunoglobulin (VH-4), or a heavy chain variable domain of a fourth immunoglobulin (VH-4) that is linked to a complementary light chain variable domain of the fourth immunoglobulin (VL-4), wherein VL-4 and VH-4 are capable of specifically binding to the fourth epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ (SEQ ID NO: 2507) to form a single-chain variable fragment; and

wherein each of VL-1 and VL-3 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_L amino acid sequence selected from any one of SEQ ID NOs: 1, 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89,

97, 105, 113, 121, 129, 145, 153, 161, 169, 177, 193, 201, 233, 241, 257, 273, 281, 289, 297, 305, 313, 321, 329, 337, 345, 353, 361, 369, 377, 385, 393, 401, 409, 417, 425, 433, 441, 449, 457, 465, 481, 489, 497, 521, 529, 537, 545, 553, 561, 609, 617, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 777, 785, 793, 801, 809, 817, 825, 833, 841, 849, 857, 865, 873, 881, 889, 945, 953, 961, 977, 985, 993, 1001, 1009, 1017, 1025, 1033, 1041, 1049, 1065, 1073, 1081, 1089, 1097, 1105, 1113, 1121, 1129, 1137, 1145, 1153, 1161, 1169, 1177, 1185, 1193, 1201, 1209, 1217, 1225, 1233, 1241, 1249, 1257, 1265, 1273, 1281, 1289, 1297, 1305, 1313, 1321, 1329, 1337, 1345, 1353, 1361, 1369, 1377, 1385, 1393, 1401, 1409, 1417, 1425, 1433, 1441, 1449, 1457, 1465, 1473, 1481, 1489, 1497, 1505, 1513, 1521, 1529, 1545, 1553, 1561, 1569, 1577, 1585, 1593, 1601, 1609, 1617, 1625, 1633, 1649, 1657, 1673, 1681, 1689, 1697, 1705, 1713, 1721, 1729, 1737, 1745, 1753, 1761, 1769, 1777, 1785, 1793, 1801, 1809, 1817, 1833, 1841, 1849, 1857, 1865, 1873, 1881, 1889, 1913, 1937, 1945, 1953, 1961, 1969, 1977, 1985, 1993, 2001, 2009, 2017, 2025, 2033, 2041, 2049, 2057, 2065, 2073, 2081, 2089, 2097, 2105, 2113, 2121, 2129, 2137, 2145, 2153, 2161, 2169, 2177, 2185, 2193, 2201, 2209, 2217, 2225, 2233, 2241, 2249, 2257, 2265, 2273, 2281, 2297, 2305, 2313, 2321, 2329, 2337 and 2345; and/or

wherein each of VH-1 and VH-3 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_H amino acid sequence selected from any one of SEQ ID NOs: 5, 13, 21, 29, 37, 45, 53, 61, 69, 77, 85, 93, 101, 109, 117, 125, 133, 149, 157, 165, 173, 181, 197, 205, 237, 245, 261, 277, 285, 293, 301, 309, 317, 325, 333, 341, 349, 357, 365, 373, 381, 389, 397, 405, 413, 421, 429, 437, 445, 453, 461, 469, 485, 493, 501, 525, 533, 541, 549, 557, 565, 613, 621, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 781, 789, 797, 805, 813, 821, 829, 837, 845, 853, 861, 869, 877, 885, 893, 949, 957, 965, 981, 989, 997, 1005, 1013, 1021, 1029, 1037, 1045, 1053, 1069, 1077, 1085, 1093, 1101, 1109, 1117, 1125, 1133, 1141, 1149, 1157, 1165, 1173, 1181, 1189, 1197, 1205, 1213, 1221, 1229, 1237, 1245, 1253, 1261, 1269, 1277, 1285, 1293, 1301, 1309, 1317, 1325, 1333, 1341, 1349, 1357, 1365, 1373, 1381, 1389, 1397, 1405, 1413, 1421, 1429, 1437, 1445, 1453, 1461, 1469, 1477, 1485, 1493, 1501, 1509, 1517, 1525, 1533, 1549, 1557, 1565, 1573, 1581, 1589, 1597, 1605, 1613, 1621, 1629, 1637, 1653, 1661, 1677, 1685, 1693, 1701, 1709, 1717, 1725, 1733, 1741, 1749, 1757, 1765, 1773, 1781, 1789, 1797, 1805, 1813, 1821, 1837, 1845, 1853, 1861, 1869, 1877, 1885, 1893, 1917, 1941, 1949, 1957, 1965, 1973, 1981, 1989, 1997, 2005, 2013, 2021, 2029, 2037, 2045, 2053, 2061, 2069, 2077, 2085, 2093, 2101, 2109, 2117, 2125, 2133, 2141, 2149, 2157, 2165, 2173, 2181, 2189, 2197, 2205, 2213, 2221, 2229, 2237, 2245, 2253, 2261, 2269, 2277, 2285, 2301, 2309, 2317, 2325, 2333, 2341, and 2349; and/or

wherein each of VL-2 and VL-4 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_L amino acid sequence selected from any one of SEQ ID NOs: 17, 25, 33, 41, 121, 137, 169, 177, 185, 193, 201, 209, 217, 225, 233, 241, 249, 257, 265, 321, 329, 337, 393, 401, 409, 473, 481, 489, 497, 505, 513, 545, 553, 561, 569, 577, 585, 593, 601, 625, 633, 641, 649, 657, 665, 673, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 785, 793, 801, 809, 817, 849, 857, 865, 873, 881, 889, 897, 905, 913, 921, 929, 937, 945, 969, 977, 1009, 1057, 1537, 1569, 1601, 1641, 1665, 1825, 1865, 1897, 1905, 1913, 1921, 1929, 2265, 2281 2289, 2329, and 2345; and/or

wherein each of V-2 and VH-4 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_H amino acid sequence selected from any one of SEQ ID NOs: 21, 29, 37, 45, 125, 141, 173, 181, 189, 197, 205, 213, 221, 229, 237, 245, 253, 261, 269, 325, 333, 341, 397, 405, 413, 477, 485, 493, 501, 509, 517, 549, 557, 565, 573, 581, 589, 597, 605, 629, 637, 645, 653, 661, 669, 677, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 789, 797, 805, 813, 821, 853, 861, 869, 877, 885, 893, 901, 909, 917, 925, 933, 941, 949, 973, 981, 1013, 1061, 1541, 1573, 1605, 1645, 1669, 1829, 1869, 1901, 1909, 1917, 1925, 1933, 2269, 2285, 2293, 2333, and 2349.

4. A heterodimeric multispecific antibody comprising a first polypeptide chain, a second polypeptide chain, a third polypeptide chain and a fourth polypeptide chain, wherein the first and second polypeptide chains are covalently bonded to one another, the second and third polypeptide chains are covalently bonded to one another, and the third and fourth polypeptide chain, and wherein:

a. the first polypeptide chain comprises in the N-terminal to C-terminal direction:
   i. a light chain variable domain of a first immunoglobulin (VL-1) that is capable of specifically binding to a first epitope;
   ii. a light chain constant domain of the first immunoglobulin (CL-1);
   iii. a flexible peptide linker comprising the amino acid sequence $(GGGGS)_3$ (SEQ ID NO: 2506); and
   iv. a light chain variable domain of a second immunoglobulin (VL-2) that is linked to a complementary heavy chain variable domain of the second immunoglobulin (VH-2), or a heavy chain variable domain of a second immunoglobulin (VH-2) that is linked to a complementary light chain variable domain of the second immunoglobulin (VL-2), wherein VL-2 and VH-2 are capable of specifically binding to a second epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ (SEQ ID NO: 2507) to form a single-chain variable fragment;

b. the second polypeptide comprises in the N-terminal to C-terminal direction:
   i. a heavy chain variable domain of the first immunoglobulin (VH-1) that is capable of specifically binding to the first epitope;
   ii. a first CH1 domain of the first immunoglobulin (CH1-1); and
   iii. a first heterodimerization domain of the first immunoglobulin, wherein the first heterodimerization domain is incapable of forming a stable homodimer with another first heterodimerization domain;

c. the third polypeptide comprises in the N-terminal to C-terminal direction:
   i. a heavy chain variable domain of a third immunoglobulin (VH-3) that is capable of specifically binding to the first epitope;
   ii. a second CH1 domain of the third immunoglobulin (CH1-3); and
   iii. a second heterodimerization domain of the third immunoglobulin, wherein the second heterodimerization domain comprises an amino acid sequence or a nucleic acid sequence that is distinct

from the first heterodimerization domain of the first immunoglobulin, wherein the second heterodimerization domain is incapable of forming a stable homodimer with another second heterodimerization domain, and wherein the second heterodimerization domain of the third immunoglobulin is configured to form a heterodimer with the first heterodimerization domain of the first immunoglobulin;

d. the fourth polypeptide comprises in the N-terminal to C-terminal direction:

i. a light chain variable domain of the third immunoglobulin (VL-3) that is capable of specifically binding to the first epitope; and

ii. a light chain constant domain of the third immunoglobulin (CL-3); and wherein VL-2 comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_L amino acid sequence selected from any one of SEQ ID NOs: 17, 25, 33, 41, 121, 137, 169, 177, 185, 193, 201, 209, 217, 225, 233, 241, 249, 257, 265, 321, 329, 337, 393, 401, 409, 473, 481, 489, 497, 505, 513, 545, 553, 561, 569, 577, 585, 593, 601, 625, 633, 641, 649, 657, 665, 673, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 785, 793, 801, 809, 817, 849, 857, 865, 873, 881, 889, 897, 905, 913, 921, 929, 937, 945, 969, 977, 1009, 1057, 1537, 1569, 1601, 1641, 1665, 1825, 1865, 1897, 1905, 1913, 1921, 1929, 2265, 2281 2289, 2329, and 2345; and/or

wherein V-2 comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a VH amino acid sequence selected from any one of SEQ ID NOs: 21, 29, 37, 45, 125, 141, 173, 181, 189, 197, 205, 213, 221, 229, 237, 245, 253, 261, 269, 325, 333, 341, 397, 405, 413, 477, 485, 493, 501, 509, 517, 549, 557, 565, 573, 581, 589, 597, 605, 629, 637, 645, 653, 661, 669, 677, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 789, 797, 805, 813, 821, 853, 861, 869, 877, 885, 893, 901, 909, 917, 925, 933, 941, 949, 973, 981, 1013, 1061, 1541, 1573, 1605, 1645, 1669, 1829, 1869, 1901, 1909, 1917, 1925, 1933, 2269, 2285, 2293, 2333, and 2349, optionally wherein both VH-1 and VH-3 comprise the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_H amino acid sequence selected from any one of SEQ ID NOs: 5, 13, 21, 29, 37, 45, 53, 61, 69, 77, 85, 93, 101, 109, 117, 125, 133, 149, 157, 165, 173, 181, 197, 205, 237, 245, 261, 277, 285, 293, 301, 309, 317, 325, 333, 341, 349, 357, 365, 373, 381, 389, 397, 405, 413, 421, 429, 437, 445, 453, 461, 469, 485, 493, 501, 525, 533, 541, 549, 557, 565, 613, 621, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 781, 789, 797, 805, 813, 821, 829, 837, 845, 853, 861, 869, 877, 885, 893, 949, 957, 965, 981, 989, 997, 1005, 1013, 1021, 1029, 1037, 1045, 1053, 1069, 1077, 1085, 1093, 1101, 1109, 1117, 1125, 1133, 1141, 1149, 1157, 1165, 1173, 1181, 1189, 1197, 1205, 1213, 1221, 1229, 1237, 1245, 1253, 1261, 1269, 1277, 1285, 1293, 1301, 1309, 1317, 1325, 1333, 1341, 1349, 1357, 1365, 1373, 1381, 1389, 1397, 1405, 1413, 1421, 1429, 1437, 1445, 1453, 1461, 1469, 1477, 1485, 1493, 1501, 1509, 1517, 1525, 1533, 1549, 1557, 1565, 1573, 1581, 1589, 1597, 1605, 1613, 1621, 1629, 1637, 1653, 1661, 1677, 1685, 1693, 1701, 1709, 1717, 1725, 1733, 1741, 1749, 1757, 1765, 1773, 1781, 1789, 1797, 1805, 1813, 1821, 1837, 1845, 1853, 1861, 1869, 1877, 1885, 1893, 1917, 1941, 1949, 1957, 1965, 1973, 1981, 1989, 1997, 2005, 2013, 2021, 2029, 2037, 2045, 2053, 2061, 2069, 2077, 2085, 2093, 2101, 2109, 2117, 2125, 2133, 2141, 2149, 2157, 2165, 2173, 2181, 2189, 2197, 2205, 2213, 2221, 2229, 2237, 2245, 2253, 2261, 2269, 2277, 2285, 2301, 2309, 2317, 2325, 2333, 2341, and 2349; and/or

wherein both VL-1 and VL-3 comprise the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_L amino acid sequence selected from any one of SEQ ID NOs: 1, 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 105, 113, 121, 129, 145, 153, 161, 169, 177, 193, 201, 233, 241, 257, 273, 281, 289, 297, 305, 313, 321, 329, 337, 345, 353, 361, 369, 377, 385, 393, 401, 409, 417, 425, 433, 441, 449, 457, 465, 481, 489, 497, 521, 529, 537, 545, 553, 561, 609, 617, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 777, 785, 793, 801, 809, 817, 825, 833, 841, 849, 857, 865, 873, 881, 889, 945, 953, 961, 977, 985, 993, 1001, 1009, 1017, 1025, 1033, 1041, 1049, 1065, 1073, 1081, 1089, 1097, 1105, 1113, 1121, 1129, 1137, 1145, 1153, 1161, 1169, 1177, 1185, 1193, 1201, 1209, 1217, 1225, 1233, 1241, 1249, 1257, 1265, 1273, 1281, 1289, 1297, 1305, 1313, 1321, 1329, 1337, 1345, 1353, 1361, 1369, 1377, 1385, 1393, 1401, 1409, 1417, 1425, 1433, 1441, 1449, 1457, 1465, 1473, 1481, 1489, 1497, 1505, 1513, 1521, 1529, 1545, 1553, 1561, 1569, 1577, 1585, 1593, 1601, 1609, 1617, 1625, 1633, 1649, 1657, 1673, 1681, 1689, 1697, 1705, 1713, 1721, 1729, 1737, 1745, 1753, 1761, 1769, 1777, 1785, 1793, 1801, 1809, 1817, 1833, 1841, 1849, 1857, 1865, 1873, 1881, 1889, 1913, 1937, 1945, 1953, 1961, 1969, 1977, 1985, 1993, 2001, 2009, 2017, 2025, 2033, 2041, 2049, 2057, 2065, 2073, 2081, 2089, 2097, 2105, 2113, 2121, 2129, 2137, 2145, 2153, 2161, 2169, 2177, 2185, 2193, 2201, 2209, 2217, 2225, 2233, 2241, 2249, 2257, 2265, 2273, 2281, 2297, 2305, 2313, 2321, 2329, 2337 and 2345.

5. (canceled)

6. A heterodimeric multispecific antibody comprising a first polypeptide chain, a second polypeptide chain, a third polypeptide chain and a fourth polypeptide chain, wherein the first and second polypeptide chains are covalently bonded to one another, the second and third polypeptide chains are covalently bonded to one another, and the third and fourth polypeptide chain, and wherein:

a. the first polypeptide chain comprises in the N-terminal to C-terminal direction:

i. a light chain variable domain of a first immunoglobulin (VL-1) that is capable of specifically binding to a first epitope;

ii. a light chain constant domain of the first immunoglobulin (CL-1);

iii. a flexible peptide linker comprising the amino acid sequence $(GGGGS)_3$ (SEQ ID NO: 2506); and

iv. a light chain variable domain of a second immunoglobulin (VL-2) that is linked to a complementary heavy chain variable domain of the second immunoglobulin (VH-2), or a heavy chain variable domain of a second immunoglobulin (VH-2) that is linked to a complementary light chain variable domain of the second immunoglobulin (VL-2), wherein VL-2 and VH-2 are capable of specifically binding to a second epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ (SEQ ID NO: 2507) to form a single-chain variable fragment;

b. the second polypeptide comprises in the N-terminal to C-terminal direction:
   i. a heavy chain variable domain of the first immunoglobulin (VH-1) that is capable of specifically binding to the first epitope;
   ii. a first CH1 domain of the first immunoglobulin (CH1-1); and
   iii. a first heterodimerization domain of the first immunoglobulin, wherein the first heterodimerization domain is incapable of forming a stable homodimer with another first heterodimerization domain;

c. the third polypeptide comprises in the N-terminal to C-terminal direction:
   i. a heavy chain variable domain of a third immunoglobulin (VH-3) that is capable of specifically binding to a third epitope;
   ii. a second CH1 domain of the third immunoglobulin (CH1-3); and
   iii. a second heterodimerization domain of the third immunoglobulin, wherein the second heterodimerization domain comprises an amino acid sequence or a nucleic acid sequence that is distinct from the first heterodimerization domain of the first immunoglobulin, wherein the second heterodimerization domain is incapable of forming a stable homodimer with another second heterodimerization domain, and wherein the second heterodimerization domain of the third immunoglobulin is configured to form a heterodimer with the first heterodimerization domain of the first immunoglobulin;

d. the fourth polypeptide comprises in the N-terminal to C-terminal direction:
   i. a light chain variable domain of the third immunoglobulin (VL-3) that is capable of specifically binding to the third epitope; and
   ii. a light chain constant domain of the third immunoglobulin (CL-3); and

wherein each of VL-1 and VL-3 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_L amino acid sequence selected from any one of SEQ ID NOs: 1, 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 105, 113, 121, 129, 145, 153, 161, 169, 177, 193, 201, 233, 241, 257, 273, 281, 289, 297, 305, 313, 321, 329, 337, 345, 353, 361, 369, 377, 385, 393, 401, 409, 417, 425, 433, 441, 449, 457, 465, 481, 489, 497, 521, 529, 537, 545, 553, 561, 609, 617, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 777, 785, 793, 801, 809, 817, 825, 833, 841, 849, 857, 865, 873, 881, 889, 945, 953, 961, 977, 985, 993, 1001, 1009, 1017, 1025, 1033, 1041, 1049, 1065, 1073, 1081, 1089, 1097, 1105, 1113, 1121, 1129, 1137, 1145, 1153, 1161, 1169, 1177, 1185, 1193, 1201, 1209, 1217, 1225, 1233, 1241, 1249, 1257, 1265, 1273, 1281, 1289, 1297, 1305, 1313, 1321, 1329, 1337, 1345, 1353, 1361, 1369, 1377, 1385, 1393, 1401, 1409, 1417, 1425, 1433, 1441, 1449, 1457, 1465, 1473, 1481, 1489, 1497, 1505, 1513, 1521, 1529, 1545, 1553, 1561, 1569, 1577, 1585, 1593, 1601, 1609, 1617, 1625, 1633, 1649, 1657, 1673, 1681, 1689, 1697, 1705, 1713, 1721, 1729, 1737, 1745, 1753, 1761, 1769, 1777, 1785, 1793, 1801, 1809, 1817, 1833, 1841, 1849, 1857, 1865, 1873, 1881, 1889, 1913, 1937, 1945, 1953, 1961, 1969, 1977, 1985, 1993, 2001, 2009, 2017, 2025, 2033, 2041, 2049, 2057, 2065, 2073, 2081, 2089, 2097, 2105, 2113, 2121, 2129, 2137, 2145, 2153, 2161, 2169, 2177, 2185, 2193, 2201, 2209, 2217, 2225, 2233, 2241, 2249, 2257, 2265, 2273, 2281, 2297, 2305, 2313, 2321, 2329, 2337 and 2345; and/or

wherein each of VH-1 and VH-3 independently comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_H amino acid sequence selected from any one of SEQ ID NOs: 5, 13, 21, 29, 37, 45, 53, 61, 69, 77, 85, 93, 101, 109, 117, 125, 133, 149, 157, 165, 173, 181, 197, 205, 237, 245, 261, 277, 285, 293, 301, 309, 317, 325, 333, 341, 349, 357, 365, 373, 381, 389, 397, 405, 413, 421, 429, 437, 445, 453, 461, 469, 485, 493, 501, 525, 533, 541, 549, 557, 565, 613, 621, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 781, 789, 797, 805, 813, 821, 829, 837, 845, 853, 861, 869, 877, 885, 893, 949, 957, 965, 981, 989, 997, 1005, 1013, 1021, 1029, 1037, 1045, 1053, 1069, 1077, 1085, 1093, 1101, 1109, 1117, 1125, 1133, 1141, 1149, 1157, 1165, 1173, 1181, 1189, 1197, 1205, 1213, 1221, 1229, 1237, 1245, 1253, 1261, 1269, 1277, 1285, 1293, 1301, 1309, 1317, 1325, 1333, 1341, 1349, 1357, 1365, 1373, 1381, 1389, 1397, 1405, 1413, 1421, 1429, 1437, 1445, 1453, 1461, 1469, 1477, 1485, 1493, 1501, 1509, 1517, 1525, 1533, 1549, 1557, 1565, 1573, 1581, 1589, 1597, 1605, 1613, 1621, 1629, 1637, 1653, 1661, 1677, 1685, 1693, 1701, 1709, 1717, 1725, 1733, 1741, 1749, 1757, 1765, 1773, 1781, 1789, 1797, 1805, 1813, 1821, 1837, 1845, 1853, 1861, 1869, 1877, 1885, 1893, 1917, 1941, 1949, 1957, 1965, 1973, 1981, 1989, 1997, 2005, 2013, 2021, 2029, 2037, 2045, 2053, 2061, 2069, 2077, 2085, 2093, 2101, 2109, 2117, 2125, 2133, 2141, 2149, 2157, 2165, 2173, 2181, 2189, 2197, 2205, 2213, 2221, 2229, 2237, 2245, 2253, 2261, 2269, 2277, 2285, 2301, 2309, 2317, 2325, 2333, 2341, and 2349; and/or

wherein VL-2 comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_L amino acid sequence selected from any one of SEQ ID NOs: 17, 25, 33, 41, 121, 137, 169, 177, 185, 193, 201, 209, 217, 225, 233, 241, 249, 257, 265, 321, 329, 337, 393, 401, 409, 473, 481, 489, 497, 505, 513, 545, 553, 561, 569, 577, 585, 593, 601, 625, 633, 641, 649, 657, 665, 673, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 785, 793, 801, 809, 817, 849, 857, 865, 873, 881, 889, 897, 905, 913, 921, 929, 937, 945, 969, 977, 1009, 1057, 1537, 1569, 1601, 1641, 1665, 1825, 1865, 1897, 1905, 1913, 1921, 1929, 2265, 2281 2289, 2329, and 2345; and/or

wherein V-2 comprises the CDR1 sequence, the CDR2 sequence and the CDR3 sequence of a V_H amino acid sequence selected from any one of SEQ ID NOs: 21, 29, 37, 45, 125, 141, 173, 181, 189, 197, 205, 213, 221, 229, 237, 245, 253, 261, 269, 325, 333, 341, 397, 405, 413, 477, 485, 493, 501, 509, 517, 549, 557, 565, 573, 581, 589, 597, 605, 629, 637, 645, 653, 661, 669, 677, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 789, 797, 805, 813, 821, 853, 861, 869, 877, 885, 893, 901, 909, 917, 925, 933, 941, 949, 973, 981, 1013, 1061, 1541, 1573, 1605, 1645, 1669, 1829, 1869, 1901, 1909, 1917, 1925, 1933, 2269, 2285, 2293, 2333, and 2349.

7. The heterodimeric multispecific antibody of claim **1**, wherein VH-1 or VH-3 comprise a V_H amino acid sequence selected from any one of SEQ ID NOs: 5, 13, 21, 29, 37, 45, 53, 61, 69, 77, 85, 93, 101, 109, 117, 125, 133, 149, 157, 165, 173, 181, 197, 205, 237, 245, 261, 277, 285, 293, 301, 309, 317, 325, 333, 341, 349, 357, 365, 373, 381, 389, 397, 405, 413, 421, 429, 437, 445, 453, 461, 469, 485, 493, 501, 525, 533, 541, 549, 557, 565, 613, 621, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 781, 789, 797, 805,

813, 821, 829, 837, 845, 853, 861, 869, 877, 885, 893, 949, 957, 965, 981, 989, 997, 1005, 1013, 1021, 1029, 1037, 1045, 1053, 1069, 1077, 1085, 1093, 1101, 1109, 1117, 1125, 1133, 1141, 1149, 1157, 1165, 1173, 1181, 1189, 1197, 1205, 1213, 1221, 1229, 1237, 1245, 1253, 1261, 1269, 1277, 1285, 1293, 1301, 1309, 1317, 1325, 1333, 1341, 1349, 1357, 1365, 1373, 1381, 1389, 1397, 1405, 1413, 1421, 1429, 1437, 1445, 1453, 1461, 1469, 1477, 1485, 1493, 1501, 1509, 1517, 1525, 1533, 1549, 1557, 1565, 1573, 1581, 1589, 1597, 1605, 1613, 1621, 1629, 1637, 1653, 1661, 1677, 1685, 1693, 1701, 1709, 1717, 1725, 1733, 1741, 1749, 1757, 1765, 1773, 1781, 1789, 1797, 1805, 1813, 1821, 1837, 1845, 1853, 1861, 1869, 1877, 1885, 1893, 1917, 1941, 1949, 1957, 1965, 1973, 1981, 1989, 1997, 2005, 2013, 2021, 2029, 2037, 2045, 2053, 2061, 2069, 2077, 2085, 2093, 2101, 2109, 2117, 2125, 2133, 2141, 2149, 2157, 2165, 2173, 2181, 2189, 2197, 2205, 2213, 2221, 2229, 2237, 2245, 2253, 2261, 2269, 2277, 2285, 2301, 2309, 2317, 2325, 2333, 2341, and 2349; and/or

wherein the VL-1 or VL-3 comprise a V_L amino acid sequence selected from any one of SEQ ID NOs: 1, 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 105, 113, 121, 129, 145, 153, 161, 169, 177, 193, 201, 233, 241, 257, 273, 281, 289, 297, 305, 313, 321, 329, 337, 345, 353, 361, 369, 377, 385, 393, 401, 409, 417, 425, 433, 441, 449, 457, 465, 481, 489, 497, 521, 529, 537, 545, 553, 561, 609, 617, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 777, 785, 793, 801, 809, 817, 825, 833, 841, 849, 857, 865, 873, 881, 889, 945, 953, 961, 977, 985, 993, 1001, 1009, 1017, 1025, 1033, 1041, 1049, 1065, 1073, 1081, 1089, 1097, 1105, 1113, 1121, 1129, 1137, 1145, 1153, 1161, 1169, 1177, 1185, 1193, 1201, 1209, 1217, 1225, 1233, 1241, 1249, 1257, 1265, 1273, 1281, 1289, 1297, 1305, 1313, 1321, 1329, 1337, 1345, 1353, 1361, 1369, 1377, 1385, 1393, 1401, 1409, 1417, 1425, 1433, 1441, 1449, 1457, 1465, 1473, 1481, 1489, 1497, 1505, 1513, 1521, 1529, 1545, 1553, 1561, 1569, 1577, 1585, 1593, 1601, 1609, 1617, 1625, 1633, 1649, 1657, 1673, 1681, 1689, 1697, 1705, 1713, 1721, 1729, 1737, 1745, 1753, 1761, 1769, 1777, 1785, 1793, 1801, 1809, 1817, 1833, 1841, 1849, 1857, 1865, 1873, 1881, 1889, 1913, 1937, 1945, 1953, 1961, 1969, 1977, 1985, 1993, 2001, 2009, 2017, 2025, 2033, 2041, 2049, 2057, 2065, 2073, 2081, 2089, 2097, 2105, 2113, 2121, 2129, 2137, 2145, 2153, 2161, 2169, 2177, 2185, 2193, 2201, 2209, 2217, 2225, 2233, 2241, 2249, 2257, 2265, 2273, 2281, 2297, 2305, 2313, 2321, 2329, 2337 and 2345, and/or

wherein VH-2 or VH-4 comprise a V_H amino acid sequence selected from any one of SEQ ID NOs: 21, 29, 37, 45, 125, 141, 173, 181, 189, 197, 205, 213, 221, 229, 237, 245, 253, 261, 269, 325, 333, 341, 397, 405, 413, 477, 485, 493, 501, 509, 517, 549, 557, 565, 573, 581, 589, 597, 605, 629, 637, 645, 653, 661, 669, 677, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 789, 797, 805, 813, 821, 853, 861, 869, 877, 885, 893, 901, 909, 917, 925, 933, 941, 949, 973, 981, 1013, 1061, 1541, 1573, 1605, 1645, 1669, 1829, 1869, 1901, 1909, 1917, 1925, 1933, 2269, 2285, 2293, 2333, and 2349; and/or

wherein VL-2 or VL-4 comprise a V_L amino acid sequence selected from any one of SEQ ID NOs: 17, 25, 33, 41, 121, 137, 169, 177, 185, 193, 201, 209, 217, 225, 233, 241, 249, 257, 265, 321, 329, 337, 393, 401, 409, 473, 481, 489, 497, 505, 513, 545, 553, 561, 569, 577, 585, 593, 601, 625, 633, 641, 649, 657, 665, 673, 681, 689, 697, 705, 713, 721, 729, 737, 745, 753, 761, 769, 785, 793, 801, 809, 817, 849, 857, 865, 873, 881, 889, 897, 905, 913, 921, 929, 937, 945, 969, 977, 1009, 1057, 1537, 1569, 1601, 1641, 1665, 1825, 1865, 1897, 1905, 1913, 1921, 1929, 2265, 2281 2289, 2329, and 2345.

8. (canceled)

9. The heterodimeric multispecific antibody of claim **1**, wherein each of VL-1 and VH-1 comprise a V_L amino acid sequence and a VH amino acid sequence selected from the group consisting of SEQ ID NOs: 1 and 5 respectively; SEQ ID NOs: 9 and 13 respectively; SEQ ID NOs: 17 and 21 respectively; SEQ ID NOs: 25 and 29 respectively; SEQ ID NOs: 33 and 37 respectively; SEQ ID NOs: 41 and 45 respectively; SEQ ID NOs: 49 and 53 respectively; SEQ ID NOs: 57 and 61 respectively; SEQ ID NOs: 73 and 77 respectively; SEQ ID NOs: 89 and 93 respectively; SEQ ID NOs: 97 and 101 respectively; SEQ ID NOs: 105 and 109 respectively; SEQ ID NOs: 113 and 117 respectively; SEQ ID NOs: 121 and 125 respectively; SEQ ID NOs: 129 and 133 respectively; SEQ ID NOs: 145 and 149 respectively; SEQ ID NOs: 161 and 165 respectively; SEQ ID NOs: 169 and 173 respectively; SEQ ID NOs: 177 and 181 respectively; SEQ ID NOs: 193 and 197 respectively; SEQ ID NOs: 201 and 205 respectively; SEQ ID NOs: 233 and 237 respectively; SEQ ID NOs: 241 and 245 respectively; SEQ ID NOs: 257 and 261 respectively; SEQ ID NOs: 273 and 277 respectively; SEQ ID NOs: 281 and 285 respectively; SEQ ID NOs: 289 and 293 respectively; SEQ ID NOs: 297 and 301 respectively; SEQ ID NOs: 305 and 309 respectively; SEQ ID NOs: 313 and 317 respectively; SEQ ID NOs: 321 and 325 respectively; SEQ ID NOs: 329 and 333 respectively; SEQ ID NOs: 337 and 341 respectively; SEQ ID NOs: 345 and 349 respectively; SEQ ID NOs: 353 and 357 respectively; SEQ ID NOs: 361 and 365 respectively; SEQ ID NOs: 369 and 373 respectively; SEQ ID NOs: 377 and 381 respectively; SEQ ID NOs: 385 and 389 respectively; SEQ ID NOs: 393 and 397 respectively; SEQ ID NOs: 401 and 405 respectively; SEQ ID NOs: 409 and 413 respectively; SEQ ID NOs: 417 and 421 respectively; SEQ ID NOs: 425 and 429 respectively; SEQ ID NOs: 433 and 437 respectively; SEQ ID NOs: 441 and 445 respectively; SEQ ID NOs: 449 and 453 respectively; SEQ ID NOs: 457 and 461 respectively; SEQ ID NOs: 465 and 469 respectively; SEQ ID NOs: 481 and 485 respectively; SEQ ID NOs: 489 and 493 respectively; SEQ ID NOs: 497 and 501 respectively; SEQ ID NOs: 521 and 525 respectively; SEQ ID NOs: 529 and 533 respectively; SEQ ID NOs: 537 and 541 respectively; SEQ ID NOs: 545 and 549 respectively; SEQ ID NOs: 553 and 557 respectively; SEQ ID NOs: 561 and 565 respectively; SEQ ID NOs: 609 and 613 respectively; SEQ ID NOs: 617 and 621 respectively; SEQ ID NOs: 681 and 685 respectively; SEQ ID NOs: 689 and 693 respectively; SEQ ID NOs: 697 and 701 respectively; SEQ ID NOs: 705 and 709 respectively; SEQ ID NOs: 713 and 717 respectively; SEQ ID NOs: 721 and 725 respectively; SEQ ID NOs: 729 and 733 respectively; SEQ ID NOs: 737 and 741 respectively; SEQ ID NOs: 745 and 749 respectively; SEQ ID NOs: 753 and 757 respectively; SEQ ID NOs: 761 and 765 respectively; SEQ ID NOs: 769 and 773 respectively; SEQ ID NOs: 785 and 789 respectively; SEQ ID NOs: 793 and 797 respectively; SEQ ID NOs: 801 and 805 respectively; SEQ ID NOs: 809 and 813 respectively; SEQ ID NOs: 817 and 821 respectively; SEQ ID NOs: 825

and 829 respectively; SEQ ID NOs: 833 and 837 respectively; SEQ ID NOs: 841 and 845 respectively; SEQ ID NOs: 849 and 853 respectively; SEQ ID NOs: 857 and 861 respectively; SEQ ID NOs: 865 and 869 respectively; SEQ ID NOs: 873 and 877 respectively; SEQ ID NOs: 881 and 885 respectively; SEQ ID NOs: 889 and 893 respectively; SEQ ID NOs: 945 and 949 respectively; SEQ ID NOs: 953 and 957 respectively; SEQ ID NOs: 961 and 965 respectively; SEQ ID NOs: 977 and 981 respectively; SEQ ID NOs: 985 and 989 respectively; SEQ ID NOs: 993 and 997 respectively; SEQ ID NOs: 1001 and 1005 respectively; SEQ ID NOs: 1009 and 1013 respectively; SEQ ID NOs: 1017 and 1021 respectively; SEQ ID NOs: 1025 and 1029 respectively; SEQ ID NOs: 1033 and 1037 respectively; SEQ ID NOs: 1041 and 1045 respectively; SEQ ID NOs: 1065 and 1069 respectively; SEQ ID NOs: 1073 and 1077 respectively; SEQ ID NOs: 1081 and 1085 respectively; SEQ ID NOs: 1089 and 1093 respectively; SEQ ID NOs: 1097 and 1101 respectively; SEQ ID NOs: 1113 and 1117 respectively; SEQ ID NOs: 1121 and 1125 respectively; SEQ ID NOs: 1129 and 1133 respectively; SEQ ID NOs: 1137 and 1141 respectively; SEQ ID NOs: 1145 and 1149 respectively; SEQ ID NOs: 1153 and 1157 respectively; SEQ ID NOs: 1161 and 1165 respectively; SEQ ID NOs: 1169 and 1173 respectively; SEQ ID NOs: 1185 and 1189 respectively; SEQ ID NOs: 1193 and 1197 respectively; SEQ ID NOs: 1201 and 1205 respectively; SEQ ID NOs: 1209 and 1213 respectively; SEQ ID NOs: 1217 and 1221 respectively; SEQ ID NOs: 1225 and 1229 respectively; SEQ ID NOs: 1233 and 1237 respectively; SEQ ID NOs: 1241 and 1245 respectively; SEQ ID NOs: 1249 and 1253 respectively; SEQ ID NOs: 1257 and 1261 respectively; SEQ ID NOs: 1265 and 1269 respectively; SEQ ID NOs: 1273 and 1277 respectively; SEQ ID NOs: 1281 and 1285 respectively; SEQ ID NOs: 1289 and 1293 respectively; SEQ ID NOs: 1297 and 1301 respectively; SEQ ID NOs: 1305 and 1309 respectively; SEQ ID NOs: 1313 and 1317 respectively; SEQ ID NOs: 1321 and 1325 respectively; 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wherein each of VL-3 and VH-3 comprise a V_L amino acid sequence and a V_H amino acid sequence selected from the group consisting of SEQ ID NOs: 1 and 5 respectively; SEQ

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1761 and 1765 respectively; SEQ ID NOs: 1769 and 1773 respectively; SEQ ID NOs: 1777 and 1781 respectively; SEQ ID NOs: 1785 and 1789 respectively; SEQ ID NOs: 1793 and 1797 respectively; SEQ ID NOs: 1801 and 1805 respectively; SEQ ID NOs: 1809 and 1813 respectively; SEQ ID NOs: 1817 and 1821 respectively; SEQ ID NOs: 1833 and 1837 respectively; SEQ ID NOs: 1841 and 1845 respectively; SEQ ID NOs: 1849 and 1853 respectively; SEQ ID NOs: 1857 and 1861 respectively; SEQ ID NOs: 1865 and 1869 respectively; SEQ ID NOs: 1873 and 1877 respectively; SEQ ID NOs: 1881 and 1885 respectively; SEQ ID NOs: 1889 and 1893 respectively; SEQ ID NOs: 1913 and 1917 respectively; SEQ ID NOs: 1937 and 1941 respectively; SEQ ID NOs: 1945 and 1949 respectively; SEQ ID NOs: 1953 and 1957 respectively; SEQ ID NOs: 1961 and 1965 respectively; SEQ ID NOs: 1969 and 1973 respectively; SEQ ID NOs: 1977 and 1981 respectively; SEQ ID NOs: 1985 and 1989 respectively; SEQ ID NOs: 1993 and 1997 respectively; SEQ ID NOs: 2001 and 2005 respectively; SEQ ID NOs: 2009 and 2013 respectively; SEQ ID NOs: 2017 and 2021 respectively; SEQ ID NOs: 2025 and 2029 respectively; SEQ ID NOs: 2033 and 2037 respectively; SEQ ID NOs: 2041 and 2045 respectively; SEQ ID NOs: 2049 and 2053 respectively; SEQ ID NOs: 2057 and 2061 respectively; SEQ ID NOs: 2065 and 2069 respectively; SEQ ID NOs: 2073 and 2077 respectively; SEQ ID NOs: 2081 and 2085 respectively; SEQ ID NOs: 2089 and 2093 respectively; SEQ ID NOs: 2097 and 2101 respectively; SEQ ID NOs: 2105 and 2109 respectively; SEQ ID NOs: 2113 and 2117 respectively; SEQ ID NOs: 2121 and 2125 respectively; SEQ ID NOs: 2129 and 2133 respectively; SEQ ID NOs: 2137 and 2141 respectively; SEQ ID NOs: 2145 and 2149 respectively; SEQ ID NOs: 2153 and 2157 respectively; SEQ ID NOs: 2161 and 2165 respectively; SEQ ID NOs: 2169 and 2173 respectively; SEQ ID NOs: 2177 and 2181 respectively; SEQ ID NOs: 2185 and 2189 respectively; SEQ ID NOs: 2193 and 2197 respectively; SEQ ID NOs: 2201 and 2205 respectively; SEQ ID NOs: 2209 and 2213 respectively; SEQ ID NOs: 2217 and 2221 respectively; SEQ ID NOs: 2225 and 2229 respectively; SEQ ID NOs: 2233 and 2237 respectively; SEQ ID NOs: 2241 and 2245 respectively; SEQ ID NOs: 2249 and 2253 respectively; SEQ ID NOs: 2257 and 2261 respectively; SEQ ID NOs: 2273 and 2277 respectively; SEQ ID NOs: 2281 and 2285 respectively; SEQ ID NOs: 2305 and 2309 respectively; SEQ ID NOs: 2313 and 2317 respectively; SEQ ID NOs: 2321 and 2325 respectively; SEQ ID NOs: 2329 and 2333 respectively; SEQ ID NOs: 2337 and 2341 respectively; and SEQ ID NOs: 2345 and 2349 respectively.

10. (canceled)

11. The heterodimeric multispecific antibody of claim **1**, wherein each of VL-1 and VH-1 comprise a V_L amino acid sequence and a V_H amino acid sequence selected from the group consisting of SEQ ID NOs: 9 and 13 respectively; SEQ ID NOs: 49 and 53 respectively; SEQ ID NOs: 57 and 61 respectively; SEQ ID NOs: 65 and 69 respectively; SEQ ID NOs: 81 and 85 respectively; SEQ ID NOs: 153 and 157 respectively; SEQ ID NOs: 161 and 165 respectively; SEQ ID NOs: 193 and 197 respectively; SEQ ID NOs: 201 and 205 respectively; SEQ ID NOs: 273 and 277 respectively; SEQ ID NOs: 281 and 285 respectively; SEQ ID NOs: 289 and 293 respectively; SEQ ID NOs: 297 and 301 respectively; SEQ ID NOs: 305 and 309 respectively; SEQ ID NOs: 313 and 317 respectively; SEQ ID NOs: 361 and 365 respectively; SEQ ID NOs: 377 and 381 respectively; SEQ ID NOs: 393 and 397 respectively; SEQ ID NOs: 401 and 405 respectively; SEQ ID NOs: 409 and 413 respectively; SEQ ID NOs: 417 and 421 respectively; SEQ ID NOs: 425 and 429 respectively; SEQ ID NOs: 433 and 437 respectively; SEQ ID NOs: 441 and 445 respectively; SEQ ID NOs: 449 and 453 respectively; SEQ ID NOs: 457 and 461 respectively; SEQ ID NOs: 465 and 469 respectively; SEQ ID NOs: 681 and 685 respectively; SEQ ID NOs: 689 and 693 respectively; SEQ ID NOs: 697 and 701 respectively; SEQ ID NOs: 705 and 709 respectively; SEQ ID NOs: 713 and 717 respectively; SEQ ID NOs: 721 and 725 respectively; SEQ ID NOs: 737 and 741 respectively; SEQ ID NOs: 745 and 749 respectively; SEQ ID NOs: 753 and 757 respectively; SEQ ID NOs: 761 and 765 respectively; SEQ ID NOs: 777 and 781 respectively; SEQ ID NOs: 825 and 829 respectively; SEQ ID NOs: 833 and 837 respectively; SEQ ID NOs: 841 and 845 respectively; SEQ ID NOs: 953 and 957 respectively; SEQ ID NOs: 961 and 965 respectively; SEQ ID NOs: 977 and 981 respectively; SEQ ID NOs: 993 and 997 respectively; SEQ ID NOs: 1001 and 1005 respectively; SEQ ID NOs: 1009 and 1013 respectively; SEQ ID NOs: 1017 and 1021 respectively; SEQ ID NOs: 1033 and 1037 respectively; SEQ ID NOs: 1049 and 1053 respectively; SEQ ID NOs: 1073 and 1077 respectively; SEQ ID NOs: 1081 and 1085 respectively; SEQ ID NOs: 1089 and 1093 respectively; SEQ ID NOs: 1105 and 1109 respectively; SEQ ID NOs: 1129 and 1133 respectively; SEQ ID NOs: 1137 and 1141 respectively; SEQ ID NOs: 1153 and 1157 respectively; SEQ ID NOs: 1161 and 1165 respectively; SEQ ID NOs: 1177 and 1181 respectively; SEQ ID NOs: 1225 and 1229 respectively; SEQ ID NOs: 1241 and 1245 respectively; SEQ ID NOs: 1257 and 1261 respectively; SEQ ID NOs: 1265 and 1269 respectively; SEQ ID NOs: 1297 and 1301 respectively; SEQ ID NOs: 1393 and 1397 respectively; SEQ ID NOs: 1409 and 1413 respectively; SEQ ID NOs: 1425 and 1429 respectively; SEQ ID NOs: 1441 and 1445 respectively; SEQ ID NOs: 1449 and 1453 respectively; SEQ ID NOs: 1457 and 1461 respectively; SEQ ID NOs: 1465 and 1469 respectively; SEQ ID NOs: 1473 and 1477 respectively; SEQ ID NOs: 1481 and 1485 respectively; SEQ ID NOs: 1497 and 1501 respectively; SEQ ID NOs: 1505 and 1509 respectively; SEQ ID NOs: 1513 and 1517 respectively; SEQ ID NOs: 1521 and 1525 respectively; SEQ ID NOs: 1529 and 1533 respectively; SEQ ID NOs: 1545 and 1549 respectively; SEQ ID NOs: 1553 and 1557 respectively; SEQ ID NOs: 1561 and 1565 respectively; SEQ ID NOs: 1569 and 1573 respectively; SEQ ID NOs: 1577 and 1581 respectively; SEQ ID NOs: 1585 and 1589 respectively; SEQ ID NOs: 1609 and 1613 respectively; SEQ ID NOs: 1617 and 1621 respectively; SEQ ID NOs: 1649 and 1653 respectively; SEQ ID NOs: 1657 and 1661 respectively; SEQ ID NOs: 1673 and 1677 respectively; SEQ ID NOs: 1689 and 1693 respectively; SEQ ID NOs: 1697 and 1701 respectively; SEQ ID NOs: 1705 and 1709 respectively; SEQ ID NOs: 1713 and 1717 respectively; SEQ ID NOs: 1721 and 1725 respectively; SEQ ID NOs: 1729 and 1733 respectively; SEQ ID NOs: 1745 and 1749 respectively; SEQ ID NOs: 1753 and 1757 respectively; SEQ ID NOs: 1761 and 1765 respectively; SEQ ID NOs: 1769 and 1773 respectively; SEQ ID NOs: 1777 and 1781 respectively; SEQ ID NOs: 1785 and 1789 respectively; SEQ ID NOs: 1793 and

1797 respectively; SEQ ID NOs: 1817 and 1821 respectively; SEQ ID NOs: 1833 and 1837 respectively; SEQ ID NOs: 1841 and 1845 respectively; SEQ ID NOs: 1849 and 1853 respectively; SEQ ID NOs: 1857 and 1861 respectively; SEQ ID NOs: 1865 and 1869 respectively; SEQ ID NOs: 1889 and 1893 respectively; SEQ ID NOs: 2257 and 2261 respectively; SEQ ID NOs: 2265 and 2269 respectively; SEQ ID NOs: 2281 and 2285 respectively; SEQ ID NOs: 2297 and 2301 respectively; SEQ ID NOs: 2305 and 2309 respectively; SEQ ID NOs: 2313 and 2317 respectively; SEQ ID NOs: 2321 and 2325 respectively; SEQ ID NOs: 2329 and 2333 respectively; SEQ ID NOs: 2337 and 2341 respectively; and SEQ ID NOs: 2345 and 2349 respectively.

12. The heterodimeric multispecific antibody of claim **1**, wherein each of VL-3 and VH-3 comprise a V_L amino acid sequence and a V_H amino acid sequence selected from the group consisting of SEQ ID NOs: 9 and 13 respectively; SEQ ID NOs: 49 and 53 respectively; SEQ ID NOs: 57 and 61 respectively; SEQ ID NOs: 65 and 69 respectively; SEQ ID NOs: 81 and 85 respectively; SEQ ID NOs: 153 and 157 respectively; SEQ ID NOs: 161 and 165 respectively; SEQ ID NOs: 193 and 197 respectively; SEQ ID NOs: 201 and 205 respectively; SEQ ID NOs: 273 and 277 respectively; SEQ ID NOs: 281 and 285 respectively; SEQ ID NOs: 289 and 293 respectively; SEQ ID NOs: 297 and 301 respectively; SEQ ID NOs: 305 and 309 respectively; SEQ ID NOs: 313 and 317 respectively; SEQ ID NOs: 361 and 365 respectively; SEQ ID NOs: 377 and 381 respectively; SEQ ID NOs: 393 and 397 respectively; SEQ ID NOs: 401 and 405 respectively; SEQ ID NOs: 409 and 413 respectively; SEQ ID NOs: 417 and 421 respectively; SEQ ID NOs: 425 and 429 respectively; SEQ ID NOs: 433 and 437 respectively; SEQ ID NOs: 441 and 445 respectively; SEQ ID NOs: 449 and 453 respectively; SEQ ID NOs: 457 and 461 respectively; SEQ ID NOs: 465 and 469 respectively; SEQ ID NOs: 681 and 685 respectively; SEQ ID NOs: 689 and 693 respectively; SEQ ID NOs: 697 and 701 respectively; SEQ ID NOs: 705 and 709 respectively; SEQ ID NOs: 713 and 717 respectively; SEQ ID NOs: 721 and 725 respectively; SEQ ID NOs: 737 and 741 respectively; SEQ ID NOs: 745 and 749 respectively; SEQ ID NOs: 753 and 757 respectively; SEQ ID NOs: 761 and 765 respectively; SEQ ID NOs: 777 and 781 respectively; SEQ ID NOs: 825 and 829 respectively; SEQ ID NOs: 833 and 837 respectively; SEQ ID NOs: 841 and 845 respectively; SEQ ID NOs: 953 and 957 respectively; SEQ ID NOs: 961 and 965 respectively; SEQ ID NOs: 977 and 981 respectively; SEQ ID NOs: 993 and 997 respectively; SEQ ID NOs: 1001 and 1005 respectively; SEQ ID NOs: 1009 and 1013 respectively; SEQ ID NOs: 1017 and 1021 respectively; SEQ ID NOs: 1033 and 1037 respectively; SEQ ID NOs: 1049 and 1053 respectively; SEQ ID NOs: 1073 and 1077 respectively; SEQ ID NOs: 1081 and 1085 respectively; SEQ ID NOs: 1089 and 1093 respectively; SEQ ID NOs: 1105 and 1109 respectively; SEQ ID NOs: 1129 and 1133 respectively; SEQ ID NOs: 1137 and 1141 respectively; SEQ ID NOs: 1153 and 1157 respectively; SEQ ID NOs: 1161 and 1165 respectively; SEQ ID NOs: 1177 and 1181 respectively; SEQ ID NOs: 1225 and 1229 respectively; SEQ ID NOs: 1241 and 1245 respectively; SEQ ID NOs: 1257 and 1261 respectively; SEQ ID NOs: 1265 and 1269 respectively; SEQ ID NOs: 1297 and 1301 respectively; SEQ ID NOs: 1393 and 1397 respectively; SEQ ID NOs: 1409 and 1413 respectively; SEQ ID NOs: 1425 and 1429 respectively; SEQ ID NOs: 1441 and 1445 respectively; SEQ ID NOs: 1449 and 1453 respectively; SEQ ID NOs: 1457 and 1461 respectively; SEQ ID NOs: 1465 and 1469 respectively; SEQ ID NOs: 1473 and 1477 respectively; SEQ ID NOs: 1481 and 1485 respectively; SEQ ID NOs: 1497 and 1501 respectively; SEQ ID NOs: 1505 and 1509 respectively; SEQ ID NOs: 1513 and 1517 respectively; SEQ ID NOs: 1521 and 1525 respectively; SEQ ID NOs: 1529 and 1533 respectively; SEQ ID NOs: 1545 and 1549 respectively; SEQ ID NOs: 1553 and 1557 respectively; SEQ ID NOs: 1561 and 1565 respectively; SEQ ID NOs: 1569 and 1573 respectively; SEQ ID NOs: 1577 and 1581 respectively; SEQ ID NOs: 1585 and 1589 respectively; SEQ ID NOs: 1609 and 1613 respectively; SEQ ID NOs: 1617 and 1621 respectively; SEQ ID NOs: 1649 and 1653 respectively; SEQ ID NOs: 1657 and 1661 respectively; SEQ ID NOs: 1673 and 1677 respectively; SEQ ID NOs: 1689 and 1693 respectively; SEQ ID NOs: 1697 and 1701 respectively; SEQ ID NOs: 1705 and 1709 respectively; SEQ ID NOs: 1713 and 1717 respectively; SEQ ID NOs: 1721 and 1725 respectively; SEQ ID NOs: 1729 and 1733 respectively; SEQ ID NOs: 1745 and 1749 respectively; SEQ ID NOs: 1753 and 1757 respectively; SEQ ID NOs: 1761 and 1765 respectively; SEQ ID NOs: 1769 and 1773 respectively; SEQ ID NOs: 1777 and 1781 respectively; SEQ ID NOs: 1785 and 1789 respectively; SEQ ID NOs: 1793 and 1797 respectively; SEQ ID NOs: 1817 and 1821 respectively; SEQ ID NOs: 1833 and 1837 respectively; SEQ ID NOs: 1841 and 1845 respectively; SEQ ID NOs: 1849 and 1853 respectively; SEQ ID NOs: 1857 and 1861 respectively; SEQ ID NOs: 1865 and 1869 respectively; SEQ ID NOs: 1889 and 1893 respectively; SEQ ID NOs: 2257 and 2261 respectively; SEQ ID NOs: 2265 and 2269 respectively; SEQ ID NOs: 2281 and 2285 respectively; SEQ ID NOs: 2297 and 2301 respectively; SEQ ID NOs: 2305 and 2309 respectively; SEQ ID NOs: 2313 and 2317 respectively; SEQ ID NOs: 2321 and 2325 respectively; SEQ ID NOs: 2329 and 2333 respectively; SEQ ID NOs: 2337 and 2341 respectively; and SEQ ID NOs: 2345 and 2349 respectively.

13. (canceled)

14. The heterodimeric multispecific antibody of claim **1**, wherein each of VL-4 and VH-4 comprise a V_L amino acid sequence and a V_H amino acid sequence selected from the group consisting of SEQ ID NOs: 17 and 21 respectively; SEQ ID NOs: 25 and 29 respectively; SEQ ID NOs: 33 and 37 respectively; SEQ ID NOs: 41 and 45 respectively; SEQ ID NOs: 121 and 125 respectively; SEQ ID NOs: 137 and 141 respectively; SEQ ID NOs: 169 and 173 respectively; SEQ ID NOs: 177 and 181 respectively; SEQ ID NOs: 185 and 189 respectively; SEQ ID NOs: 193 and 197 respectively; SEQ ID NOs: 201 and 205 respectively; SEQ ID NOs: 209 and 213 respectively; SEQ ID NOs: 217 and 221 respectively; SEQ ID NOs: 225 and 229 respectively; SEQ ID NOs: 233 and 237 respectively; SEQ ID NOs: 241 and 245 respectively; SEQ ID NOs: 249 and 253 respectively; SEQ ID NOs: 257 and 261 respectively; SEQ ID NOs: 265 and 269 respectively; SEQ ID NOs: 321 and 325 respectively; SEQ ID NOs: 329 and 333 respectively; SEQ ID NOs: 337 and 341 respectively; SEQ ID NOs: 393 and 397 respectively; SEQ ID NOs: 401 and 405 respectively; SEQ ID NOs: 409 and 413 respectively; SEQ ID NOs: 473 and 477 respectively; SEQ ID NOs: 481 and 485 respectively;

SEQ ID NOs: 489 and 493 respectively; SEQ ID NOs: 497 and 501 respectively; SEQ ID NOs: 505 and 509 respectively; SEQ ID NOs: 513 and 517 respectively; SEQ ID NOs: 545 and 549 respectively; SEQ ID NOs: 553 and 557 respectively; SEQ ID NOs: 561 and 565 respectively; SEQ ID NOs: 569 and 573 respectively; SEQ ID NOs: 577 and 581 respectively; SEQ ID NOs: 585 and 589 respectively; SEQ ID NOs: 593 and 597 respectively; SEQ ID NOs: 601 and 605 respectively; SEQ ID NOs: 625 and 629 respectively; SEQ ID NOs: 633 and 637 respectively; SEQ ID NOs: 641 and 645 respectively; SEQ ID NOs: 649 and 653 respectively; SEQ ID NOs: 657 and 661 respectively; SEQ ID NOs: 665 and 669 respectively; SEQ ID NOs: 673 and 677 respectively; SEQ ID NOs: 681 and 685 respectively; SEQ ID NOs: 689 and 693 respectively; SEQ ID NOs: 697 and 701 respectively; SEQ ID NOs: 705 and 709 respectively; SEQ ID NOs: 713 and 717 respectively; SEQ ID NOs: 721 and 725 respectively; SEQ ID NOs: 729 and 733 respectively; SEQ ID NOs: 737 and 741 respectively; SEQ ID NOs: 745 and 749 respectively; SEQ ID NOs: 753 and 757 respectively; SEQ ID NOs: 761 and 765 respectively; SEQ ID NOs: 769 and 773 respectively; SEQ ID NOs: 785 and 789 respectively; SEQ ID NOs: 793 and 797 respectively; SEQ ID NOs: 801 and 805 respectively; SEQ ID NOs: 809 and 813 respectively; SEQ ID NOs: 817 and 821 respectively; SEQ ID NOs: 849 and 853 respectively; SEQ ID NOs: 857 and 861 respectively; SEQ ID NOs: 865 and 869 respectively; SEQ ID NOs: 873 and 877 respectively; SEQ ID NOs: 881 and 885 respectively; SEQ ID NOs: 889 and 893 respectively; SEQ ID NOs: 897 and 901 respectively; SEQ ID NOs: 905 and 909 respectively; SEQ ID NOs: 913 and 917 respectively; SEQ ID NOs: 921 and 925 respectively; SEQ ID NOs: 929 and 933 respectively; SEQ ID NOs: 937 and 941 respectively; SEQ ID NOs: 945 and 949 respectively; SEQ ID NOs: 969 and 973 respectively; SEQ ID NOs: 977 and 981 respectively; SEQ ID NOs: 1009 and 1013 respectively; SEQ ID NOs: 1057 and 1061 respectively; SEQ ID NOs: 1537 and 1541 respectively; SEQ ID NOs: 1569 and 1573 respectively; SEQ ID NOs: 1601 and 1605 respectively; SEQ ID NOs: 1641 and 1645 respectively; SEQ ID NOs: 1665 and 1669 respectively; SEQ ID NOs: 1825 and 1829 respectively; SEQ ID NOs: 1865 and 1869 respectively; SEQ ID NOs: 1897 and 1901 respectively; SEQ ID NOs: 1905 and 1909 respectively; SEQ ID NOs: 1913 and 1917 respectively; SEQ ID NOs: 1921 and 1925 respectively; SEQ ID NOs: 1929 and 1933 respectively; SEQ ID NOs: 2265 and 2269 respectively; SEQ ID NOs: 2281 and 2285 respectively; 2289 and 2293 respectively; 2329 and 2333 respectively; and SEQ ID NOs: 2345 and 2349, respectively.

15. The heterodimeric multispecific antibody of claim **1**, wherein the first immunoglobulin or the third immunoglobulin

binds to a cell surface antigen selected from the group consisting of a2b b3 (Glycoprotein IIb/IIIa), a4, a4b7, a4b7+aEb7, a5, Activin receptor type-2B, ALK1, Alpha-synuclein, amyloid beta, APP, AXL, Blood Group A, CAIX, CCL-2, CD105 (endoglin), CD115 (CSF1R), CD116a (CSF2Ra), CD123, CD152 (CTLA4), CD184 (CXCR4), CD19, CD192 (CCR2), CD194 (CCR4), CD195 (CCR5), CD20, CD200, CD22, CD221 (IGF1R), CD248, CD25, CD257 (BAFF), CD26, CD262 (DR5), CD276 (B7H3), CD3, CD30 (TNFRSF8), CD319 (SLAMF7), CD33, CD332 (FGFR2), CD350 (FZD10), CD37, CD371 (CLEC12A), CD38, CD4, CD49b (a2), CD51 (a5), CD52, CD56, CD61 (a4b3), CD70, CD73 (NTSE), CD74, CEA, Claudin-18.2, cMET, CRLR, DLL3, DLL4, DNA/histone (H1) complex, EGFR, EpCAM, EGFR-HER3, EGFRvIII, EphA3, ERGT(GalNAc) Tn Antigen, FLT1, FOLR1, frizzled family receptor (FZD), Lewis Y, Lewis X, GCGR, GD2, GD2 α-acetyl, GD3, GM1, GM1 fucosyl, GM2, GPA33, GPNMB, GUCY2C, HER2, HER3, HGFR (cMET), IgHe, IGLF2, Kallikreins, LINGO1, LOXL2, Ly6/PLAUR domain-containing protein 3, MADCAM1, MAG, Mesothelin, MT1-MMP (MMP14), MUC1, Mucin SAC, NaPi2b, NeuGc-GM3, notch, NOTCH2/NOTCH3 receptors, oxLDL, P-selectin, PCSK9, PDGFRA, PDGFRa, phosphatidylserine, polysialic acid, PSMA, PVRL4, RGMA, CD240D Blood group D antigen, root plate-specific spondin 3, serum amyloid P component, STEAP-1, TACSTD2, TGFb, TWEAKR, TYRP1, VEGFR2, VSIR, CD171 (L1CAM), CD19, CD47, pMHC[NY-ESO1], pMHC[MART1], pMHC[MAGEA1], pMHC[Tyrosinase], pMHC[gp100], pMHC[MUC1], pMHC[tax], pMHC[WT-1], pMHC[EBNA-1], pMHC[LMP2], pMHC[hTERT], GPC3, CD80, CD23, and fibronectin extra domain-B, or

bind to two different epitopes on a target cell, optionally wherein the target cell is a cancer cell.

16. (canceled)

17. (canceled)

18. The heterodimeric multispecific antibody of claim **1**, wherein the second immunoglobulin or the fourth immunoglobulin

bind to an epitope on a white blood cell, a monocyte, a lymphocyte, a granulocyte, a macrophage, a T cell, a NK cell, a B cell, a NKT cell, an ILC, or neutrophil, or

bind to an antigen selected from the group consisting of Dabigatran, a4, a4b7, a4b7 +aEb7, a5, AXL, BnDOTA, CD11a (LFA-1), CD3, CD4, CD8, CD16, CD19, CD22, CD23, CD25, CD28, CD30 (TNFRSF8), CD33, CD38, CD40, CD40L, CD47, CD49b (a2), CD54 (ICAM-1), CD56, CD74, CD80, CD115 (CSF1R), CD116a (CSF2Ra), CD123, CD134 (OX40), CD137 (41BB), CD152 (CTLA4), CD184 (CXCR4), CD192 (CCR2), CD194 (CCR4), CD195 (CCR5), CD223 (LAG-3), CD252 (OX40L), CD254 (RANKL), CD262 (DR5), CD27, CD200, CD221 (IGF1R), CD248, CD274 (PD-L1), CD275 (ICOS-L), CD278 (ICOS), CD279 (PD-1), CD319 (SLAMF7), CD371 (CLEC12A), MADCAM1, MT1-MMP (MMP14), NKG2A, NRP1,TIGIT, VSIR, KIRDL1/2/3, and KIR2DL2, or

bind to two different epitopes on a white blood cell, a monocyte, a lymphocyte, a granulocyte, a macrophage, a T cell, a NK cell, a B cell, a NKT cell, an ILC, or neutrophil.

19. (canceled)

20. (canceled)

21. The heterodimeric multispecific antibody of claim **1**, wherein

the second immunoglobulin binds CD3 and the fourth immunoglobulin binds an immune cell receptor selected from the group consisting of CD4, CD8, CD25, CD28, CTLA4, OX40, ICOS, PD-1, PD-L1, 41BB, CD2, CD69, and CD45, or

the second immunoglobulin binds CD16 and the fourth immunoglobulin binds an immune cell receptor selected from the group consisting of CD56, NKG2D, and KIRDL1/2/3, or

wherein the fourth immunoglobulin binds to an agent selected from the group consisting of a cytokine, a nucleic acid, a hapten, a small molecule, a radionuclide, an immunotoxin, a vitamin, a peptide, a lipid, a carbohydrate, biotin, digoxin, or any conjugated variants thereof, or

wherein the antibody is a monoclonal antibody, a chimeric antibody, or a humanized antibody.

22. (canceled)

23. (canceled)

24. The heterodimeric multispecific antibody of claim **1**, wherein the first immunoglobulin and the third immunoglobulin

bind to their respective epitopes with a monovalent affinity or an effective affinity between about 100 nM to about 100 pM, or

bind to cell surface epitopes that are between 60 and 120 angstroms apart, or

bind to their respective epitopes with a monovalent affinity or an effective affinity that is less than 100 pM, or

bind to cell surface epitopes that are up to 180 angstroms apart.

25. (canceled)

26. (canceled)

27. (canceled)

28. The heterodimeric multispecific antibody of claim **1**, wherein the first heterodimerization domain and/or the second heterodimerization domain is a CH2-CH3 domain and has an isotype selected from the group consisting of IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgM, IgD, and IgE, optionally wherein

the first heterodimerization domain and/or the second heterodimerization domain is an IgG1 constant region comprising one or more amino acid substitutions selected from the group consisting of N297A and K322A, or

the first heterodimerization domain is a CH2-CH3 domain comprising a K409R mutation and the second heterodimerization domain is a CH2-CH3 domain comprising a F405L mutation.

29. (canceled)

30. (canceled)

31. (canceled)

32. A recombinant nucleic acid sequence encoding the heterodimeric multispecific antibody of claim **1**.

33. A host cell or vector comprising the recombinant nucleic acid sequence of claim **32**.

34. A composition comprising the heterodimeric multispecific antibody of claim **1** and a pharmaceutically-acceptable carrier, wherein the antibody is optionally conjugated to an agent selected from the group consisting of isotopes, dyes, chromagens, contrast agents, drugs, toxins, cytokines, enzymes, enzyme inhibitors, hormones, hormone antagonists, growth factors, radionuclides, metals, liposomes, nanoparticles, RNA, DNA or any combination thereof.

35. A method for treating cancer in a subject in need thereof, comprising administering to the subject an effective amount of the heterodimeric multispecific antibody of claim **1**, optionally wherein

the cancer is selected from the group consisting of lung cancer, colorectal cancer, skin cancer, breast cancer, ovarian cancer, leukemia, pancreatic cancer, and gastric cancer, or

the heterodimeric multispecific antibody is administered to the subject separately, sequentially or simultaneously with an additional therapeutic agent.

36. (canceled)

37. (canceled)

38. A kit comprising the heterodimeric multispecific antibody of claim **1**, and instructions for use.

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