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(54) **METHODS OF USING BISPECIFIC ANTIGEN-BINDING CONSTRUCTS TARGETING HER2**

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§ 371 (c)(1),
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A61K 47/68	(2006.01)
C07K 16/28	(2006.01)

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

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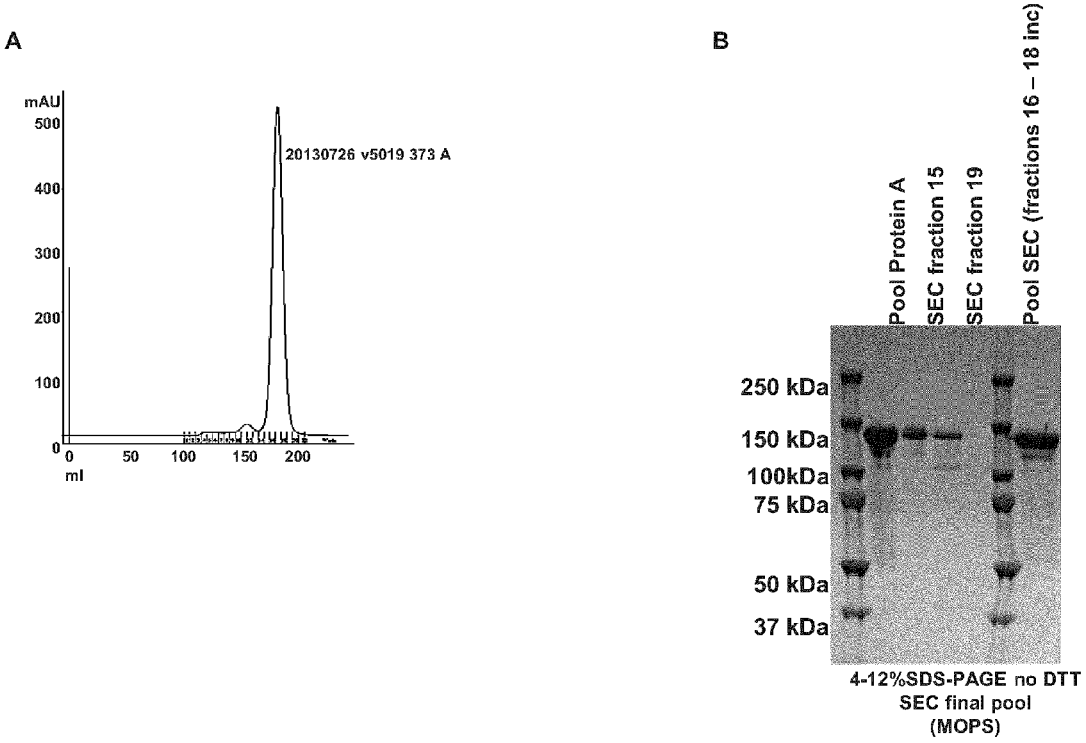
(57) **ABSTRACT**

Described herein methods of using antigen-binding constructs to treat HER2+ tumors in a subject such as breast, lung, or head and neck tumors. In some aspects, the tumor volume in the subject after receiving at least seven doses of the antigen binding construct is less than the tumor volume of a control subject receiving an equivalent amount of trastuzumab. In some aspects, the survival of the subject receiving the antigen binding construct is increased as compared to a control subject receiving an equivalent amount of a non-specific control antibody or as compared to a control subject not receiving treatment.



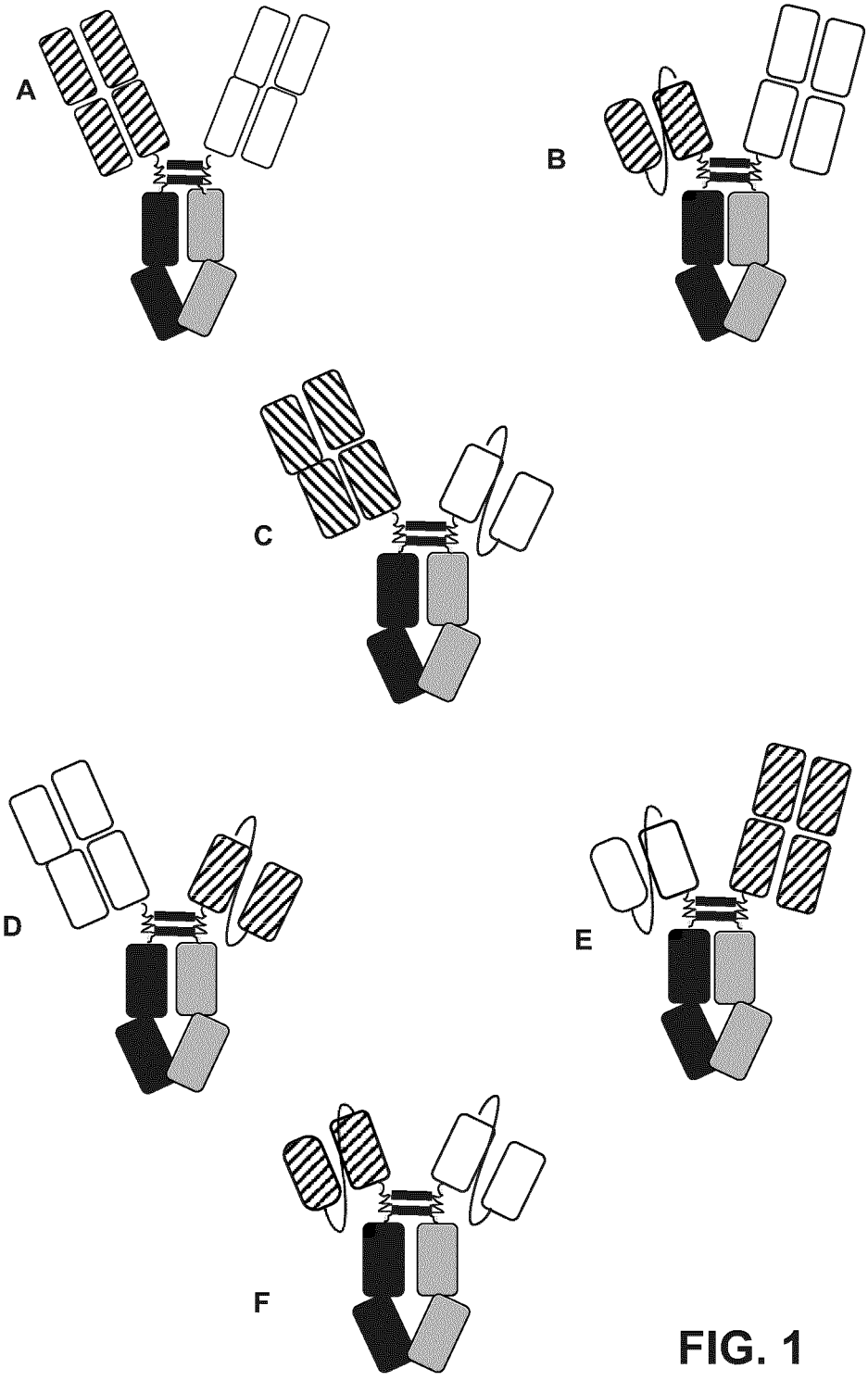


FIG. 1

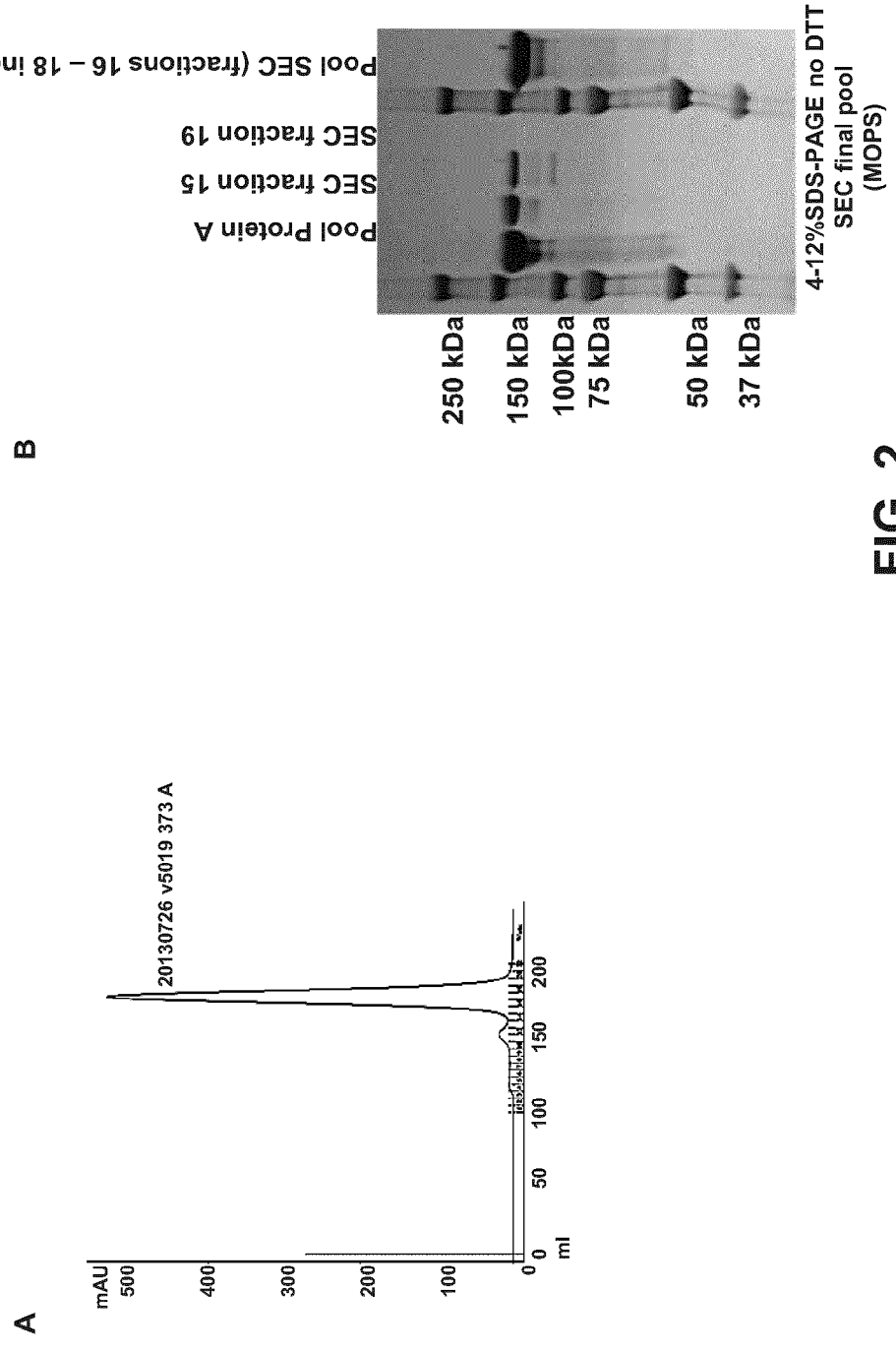

A
20130726 v5019 373 A
mAU
500
400
300
200
100
0
50
100
150
200
ml
B
4-12%SDS-PAGE no DTT
SEC final pool
(MOPS)
250 kDa
150 kDa
100kDa
75 kDa
50 kDa
37 kDa
Pool Protein A
SEC fraction 15
SEC fraction 19
Pool SEC (fractions 16 – 18 inc)

FIG. 2

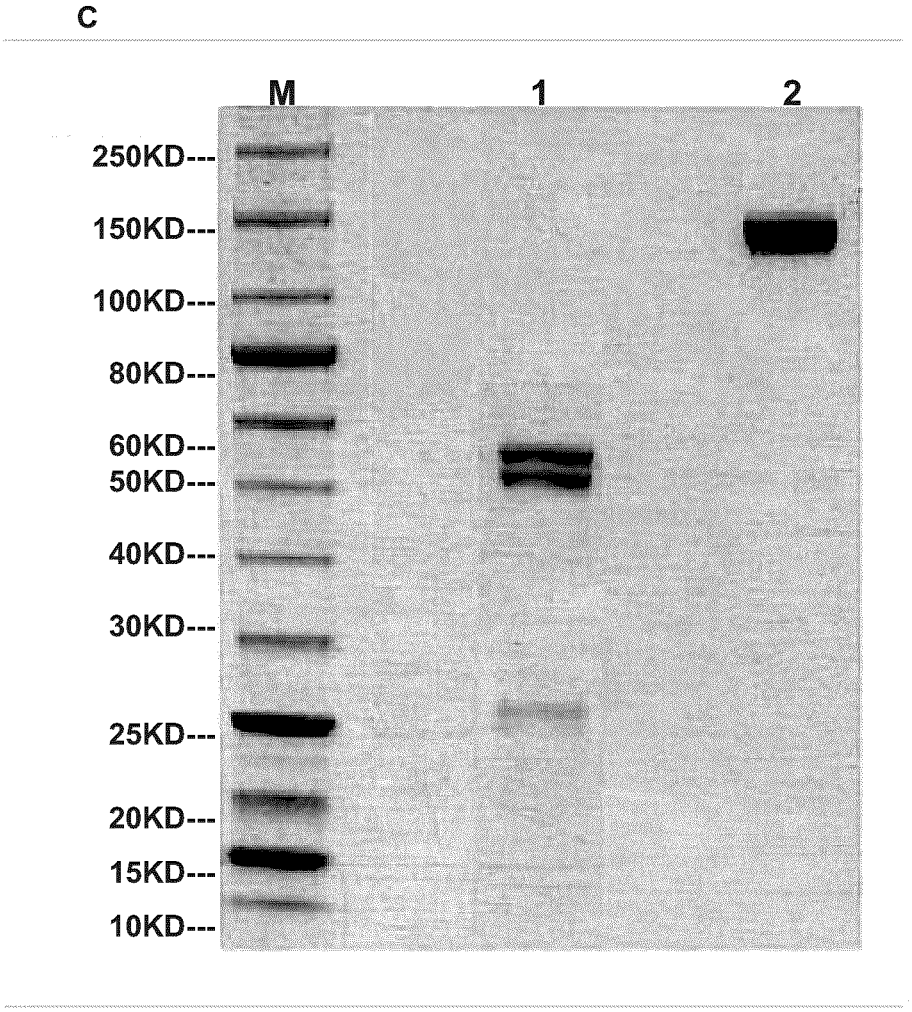
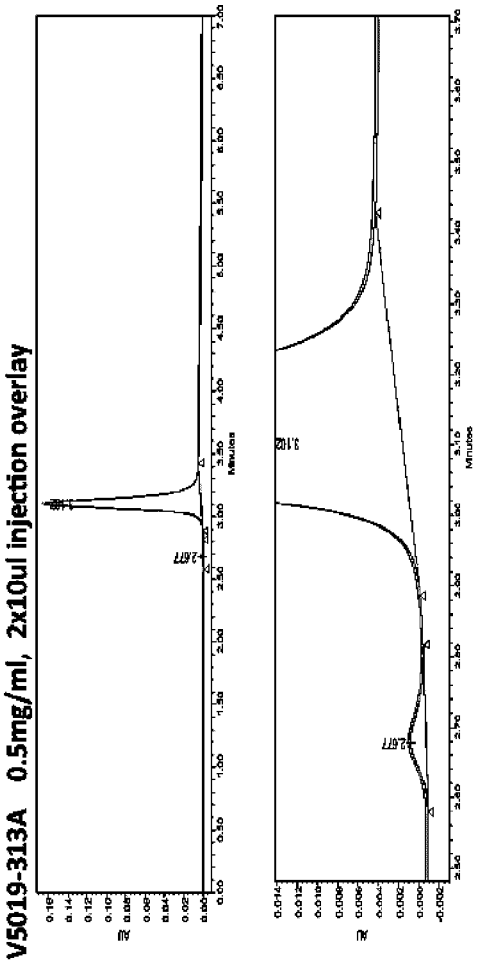
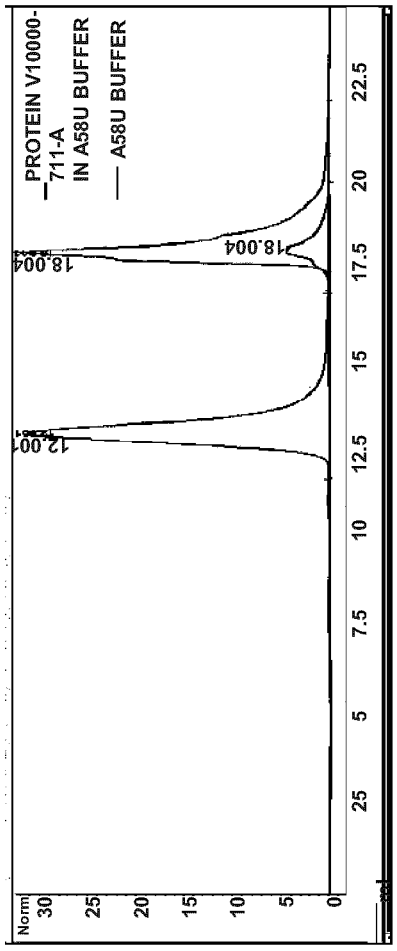

C
M
1
2
250KD---
150KD---
100KD---
80KD---
60KD---
50KD---
40KD---
30KD---
25KD---
20KD---
15KD---
10KD---

FIG. 2 (Cont'd...)



v5019-313A	est MW	log MW	Ret time	% peak area
peak 1	300902	5.478426	2.677	0.83
	298938	5.475581	2.680	0.82
peak 2	118957	5.075391	3.102	99.17
	118957	5.075391	3.102	99.18

FIG. 3A



Peak #	RT (min)	Type	Height	Area	Area%
1	8.022	MF R	0.183	22.103	1.508
2	11.059	MF R	0.179	9.708	0.662
3	12.961	MF R	30.701	1416.498	96.619
4	15.419	FM R	0.299	17.759	1.211

FIG. 3B

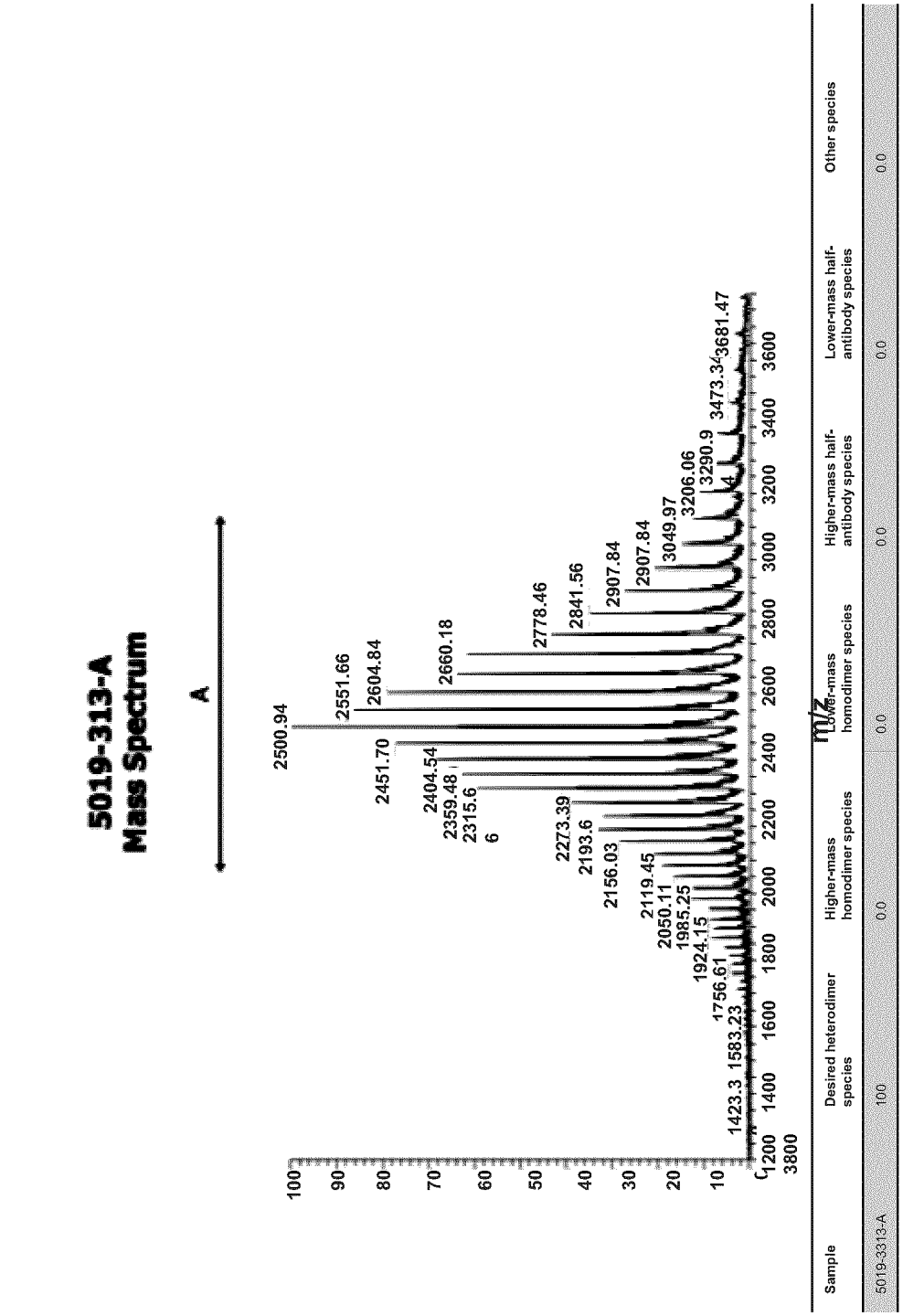

5019-313-A
Mass Spectrum
A
m/z
Sample
Desired heterodimer species
Higher-mass homodimer species
Lower-mass homodimer species
Higher-mass half-antibody species
Lower-mass half-antibody species
Other species
5019-3313-A
100
0.0
0.0
0.0
0.0
0.0

FIG. 4A

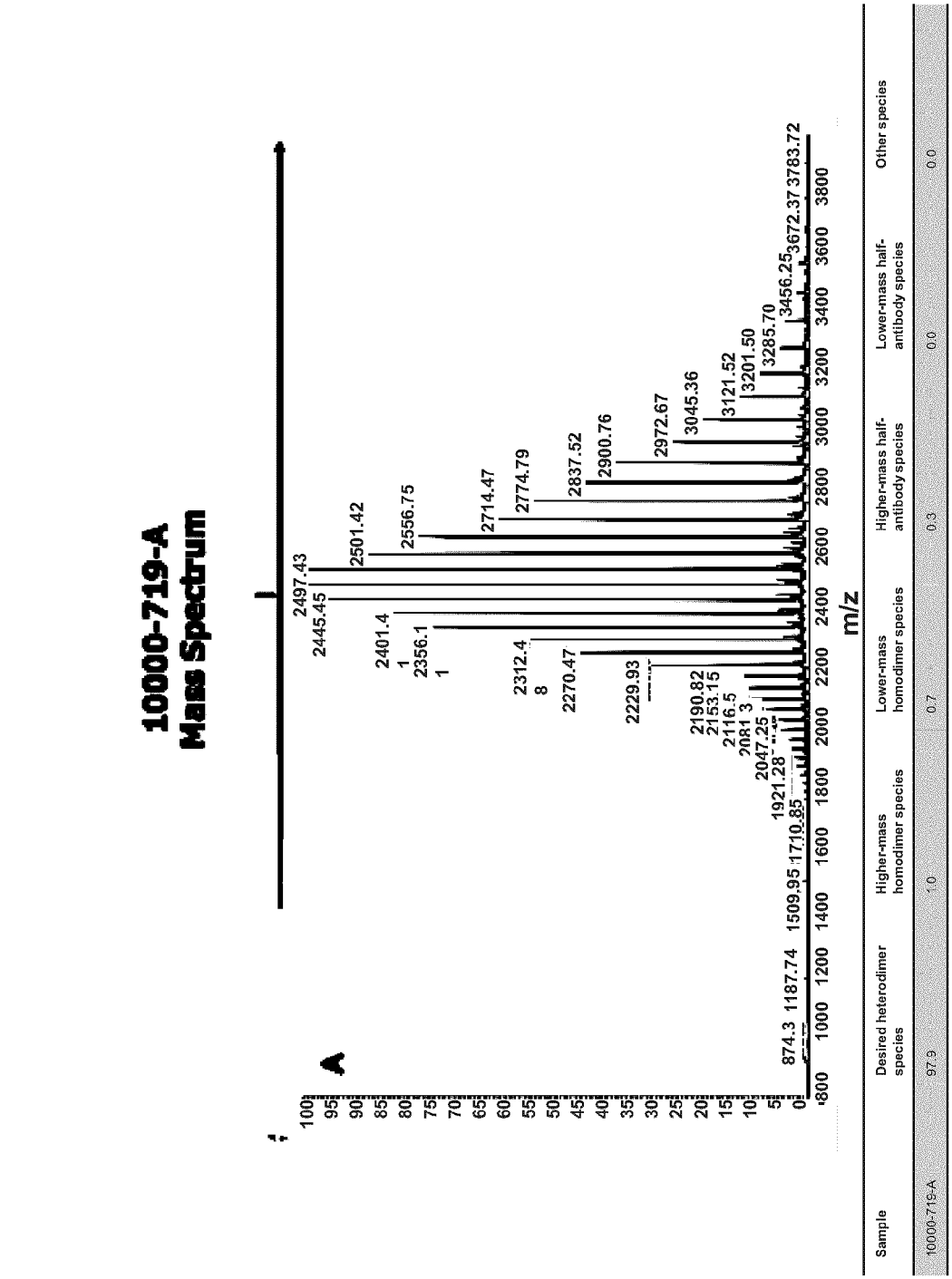

10000-719-A
Mass Spectrum
A
%
m/z
2497.43
2445.45
2501.42
2401.4
1
2556.75
2356.1
1
2714.47
2774.79
2312.4
8
2837.52
2270.47
2900.76
2229.93
2972.67
3045.36
2190.82
2153.15
2116.5
2081.3
3121.52
3201.50
2047.25
1921.28
3285.70
1710.85
3456.25
1509.95
3672.37
3783.72
1187.74
874.3
800
1000
1200
1400
1600
1800
2000
2200
2400
2600
2800
3000
3200
3400
3600
3800
Sample
Desired heterodimer species
Higher-mass homodimer species
Lower-mass homodimer species
Higher-mass half-antibody species
Lower-mass half-antibody species
Other species
10000-719-A
97.9
1.0
0.7
0.3
0.0
0.0

FIG. 4B

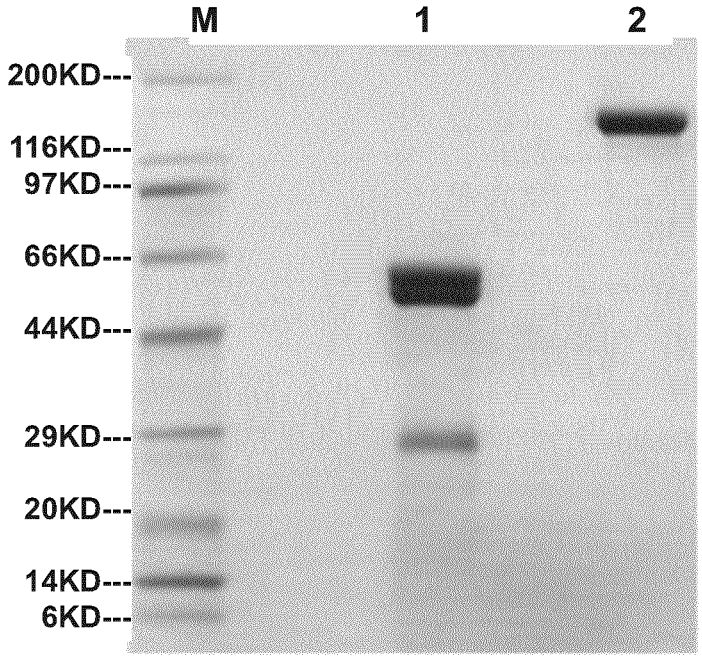
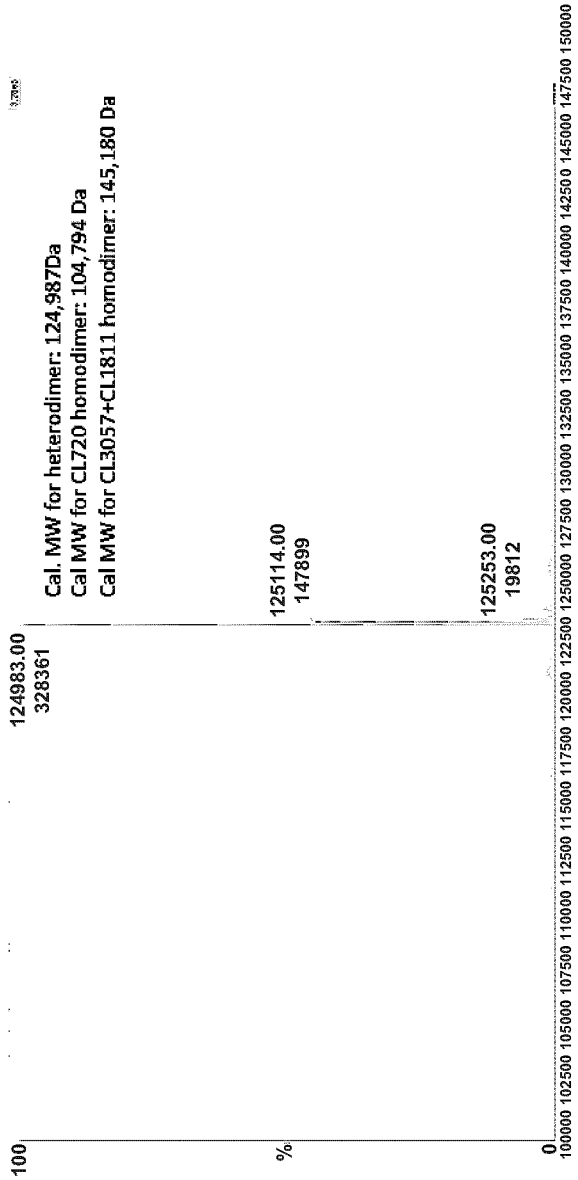


FIG. 5A



	Amount of Each Species as a Percentage of All Quantified				
	Heterodimer	CH-A Homodimer	CH-B Homodimer	CH-B Monomer	CH-A Half-antibody
v5019	99.4	0.3	0.1	0	0.2

*: Lysine and O-glycan side peaks were not included in this calculation

FIG. 5B

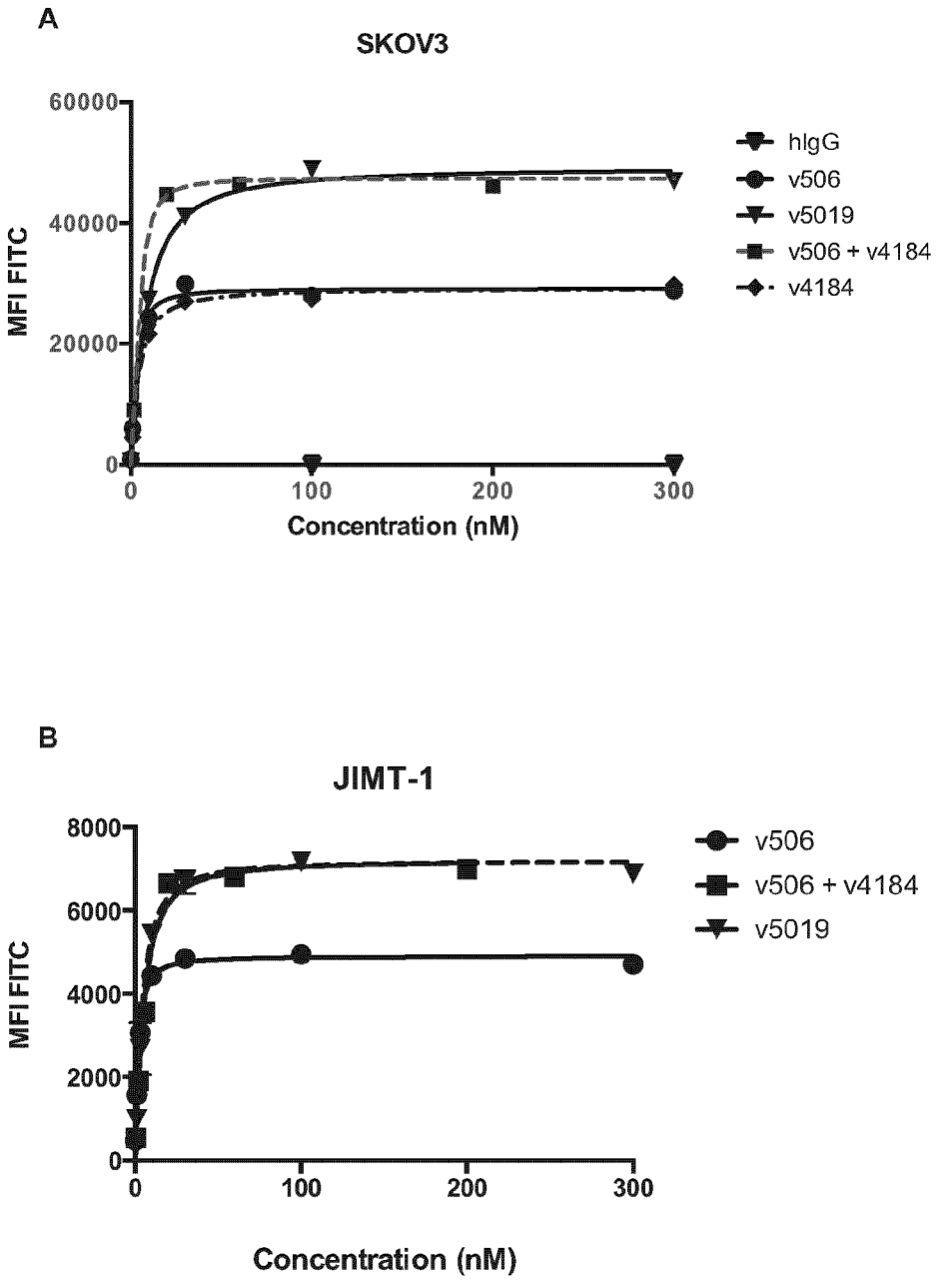
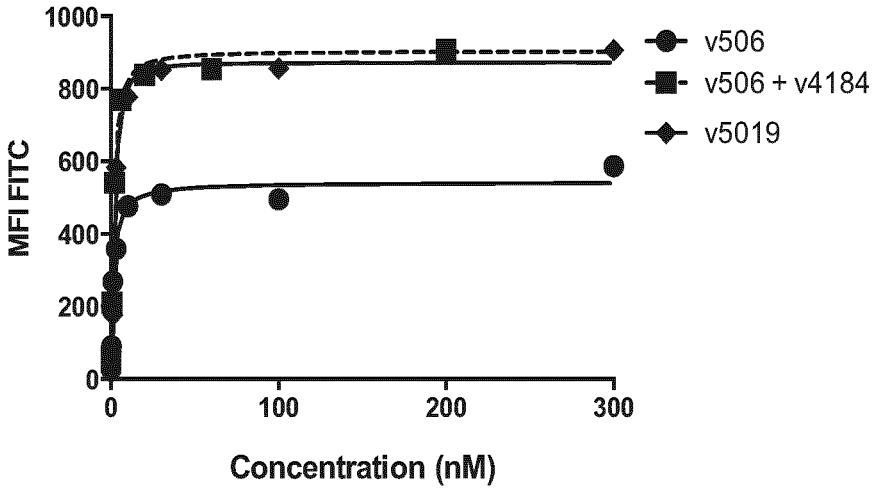

A
SKOV3
60000
40000
20000
0
MFI FITC
0
100
200
300
Concentration (nM)
hIgG
v506
v5019
v506 + v4184
v4184
B
JIMT-1
8000
6000
4000
2000
0
MFI FITC
0
100
200
300
Concentration (nM)
v506
v506 + v4184
v5019

FIG. 6

C



D

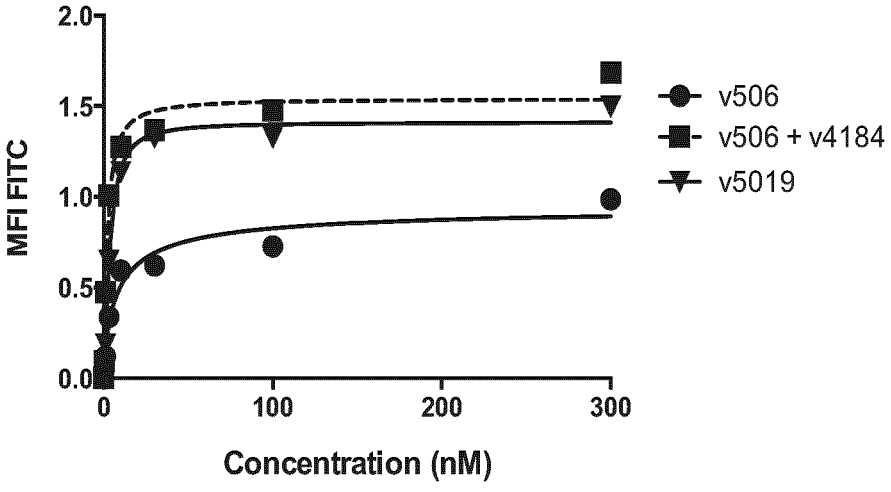
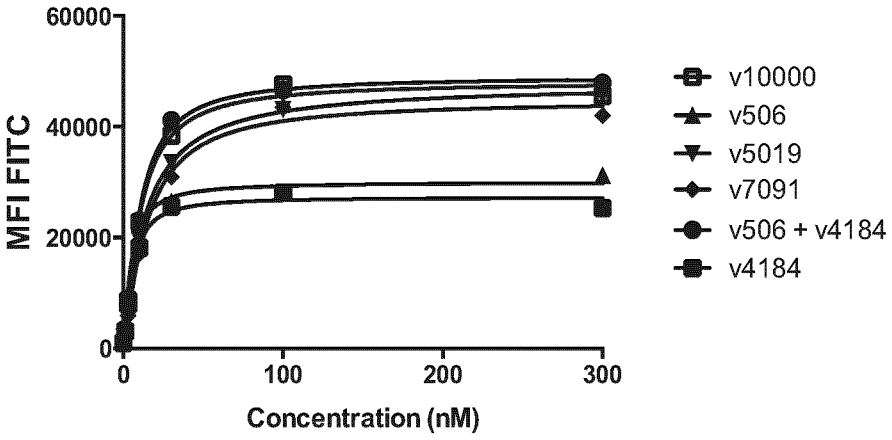


FIG. 6 (Cont'd...)

E



F

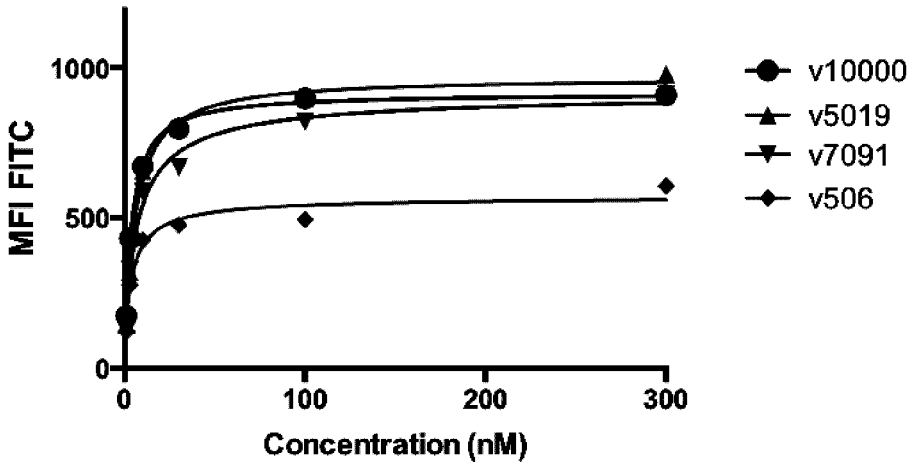


FIG. 6 (Cont'd...)

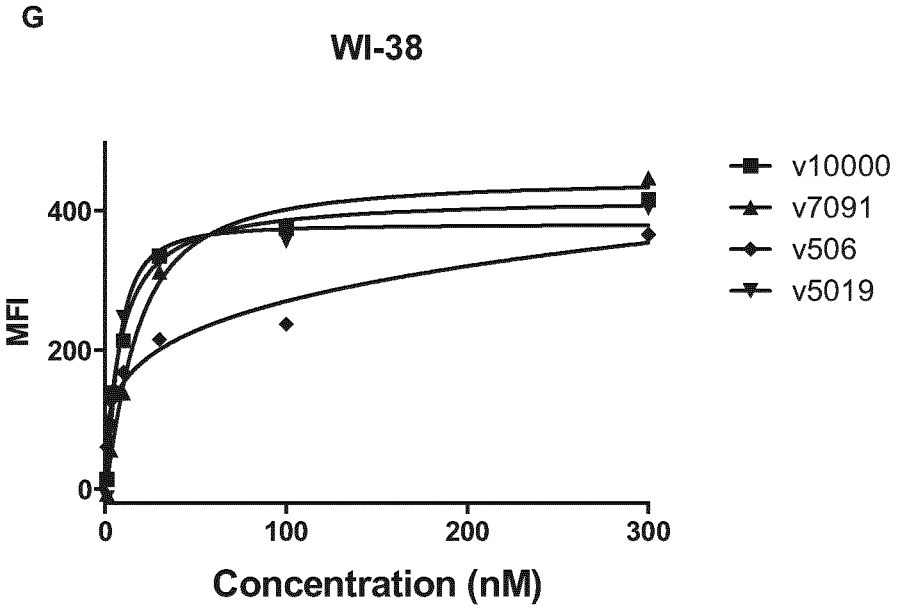
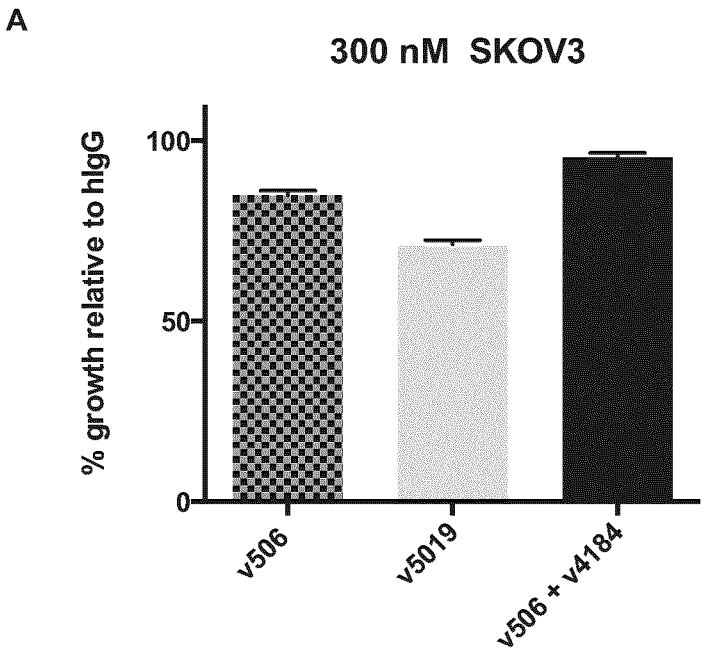

G
WI-38
MFI
400
200
0
0
100
200
300
Concentration (nM)
v10000
v7091
v506
v5019

FIG. 6 (Cont'd...)


A
300 nM SKOV3
% growth relative to hIgG
100
50
0
v506
v5019
v506 + v4184

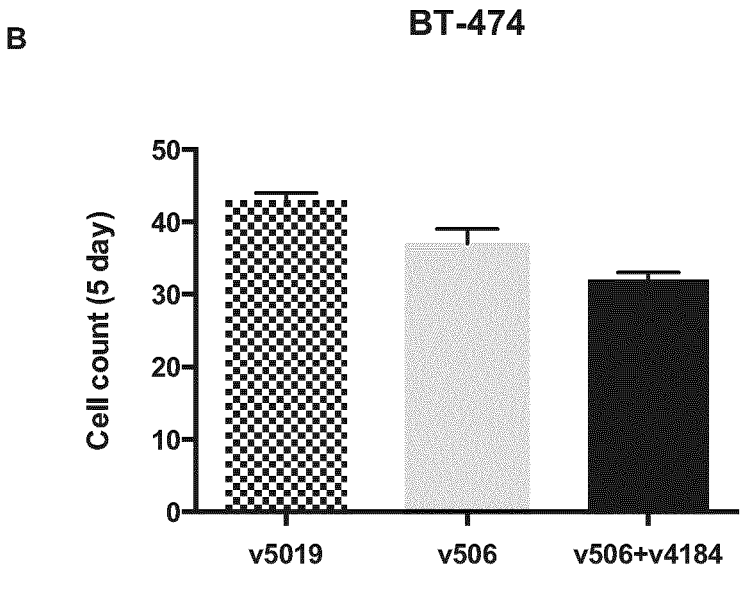

B
BT-474
Cell count (5 day)
50
40
30
20
10
0
v5019
v506
v506+v4184

FIG. 7

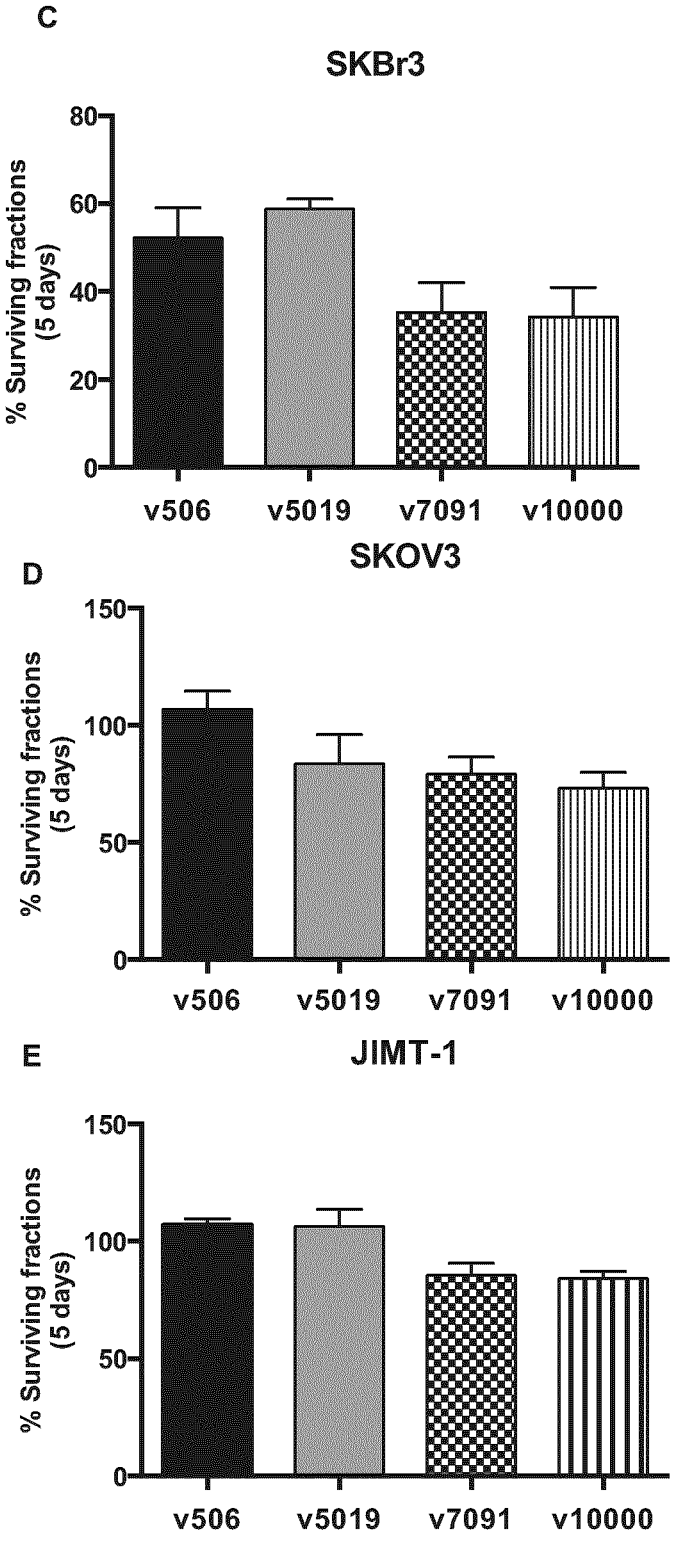

C
SKBr3
% Surviving fractions (5 days)
80
60
40
20
0
v506
v5019
v7091
v10000
D
SKOV3
% Surviving fractions (5 days)
150
100
50
0
v506
v5019
v7091
v10000
E
JIMT-1
% Surviving fractions (5 days)
150
100
50
0
v506
v5019
v7091
v10000

FIG. 7 (Cont'd...)

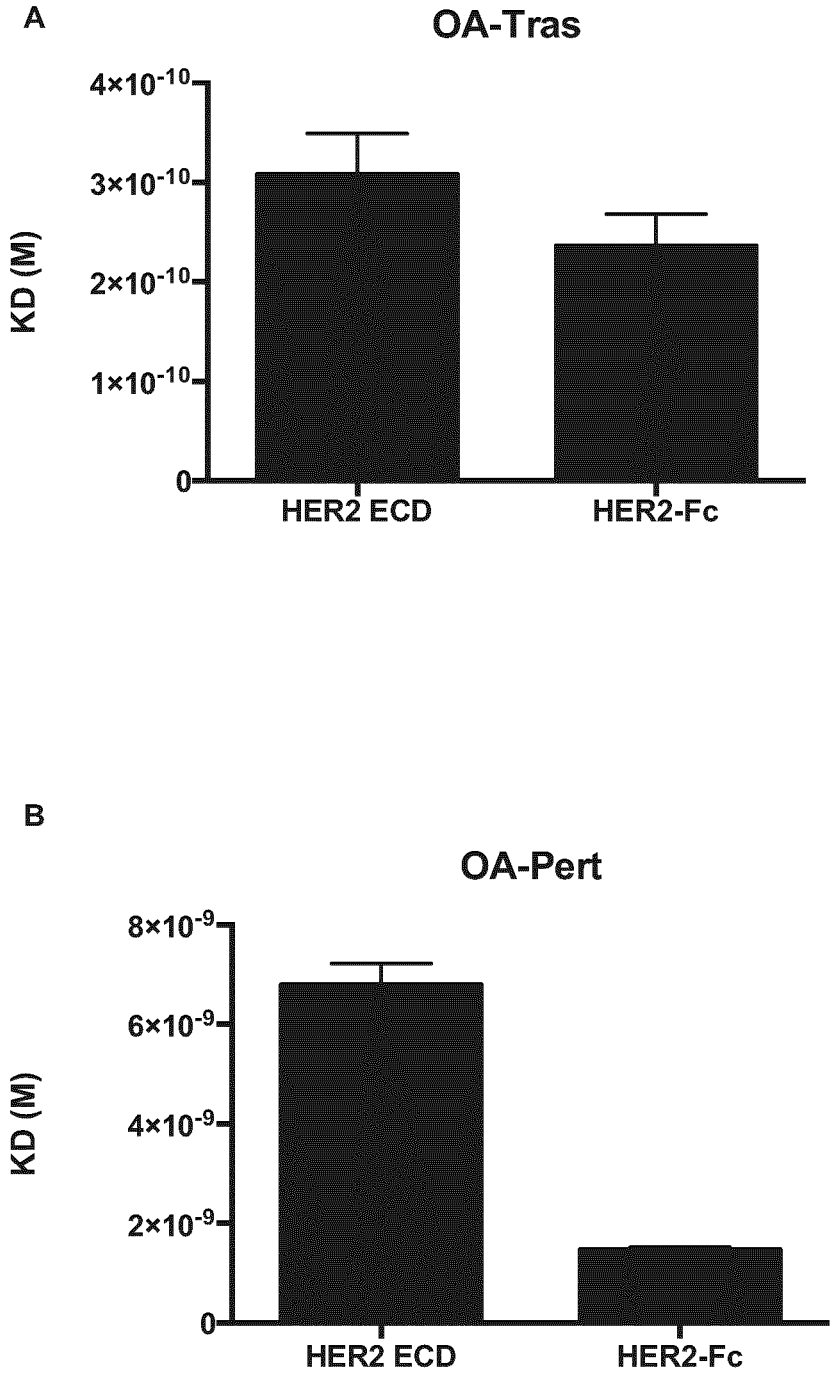
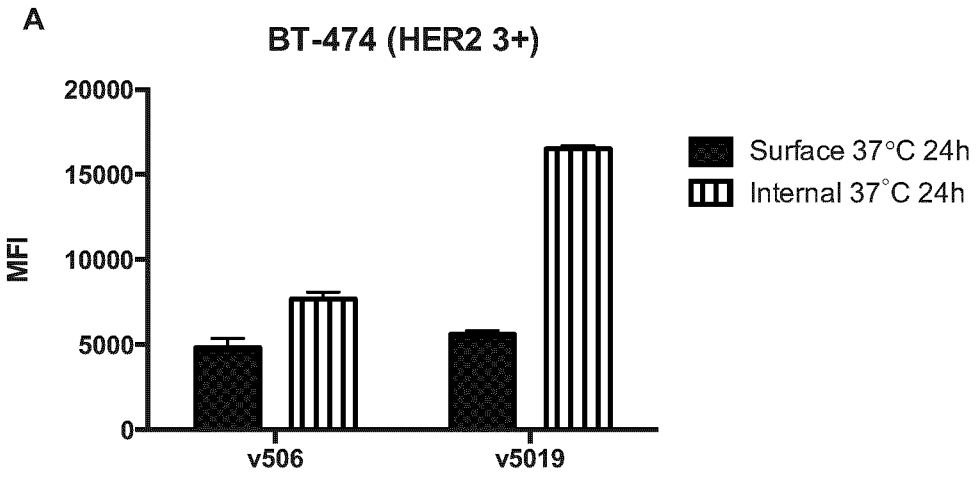

A
OA-Tras
KD (M)
4×10-10
3×10-10
2×10-10
1×10-10
0
HER2 ECD
HER2-Fc
B
OA-Pert
KD (M)
8×10-9
6×10-9
4×10-9
2×10-9
0
HER2 ECD
HER2-Fc

FIG. 8


A
BT-474 (HER2 3+)
20000
15000
10000
5000
0
MFI
v506
v5019
Surface 37°C 24h
Internal 37°C 24h

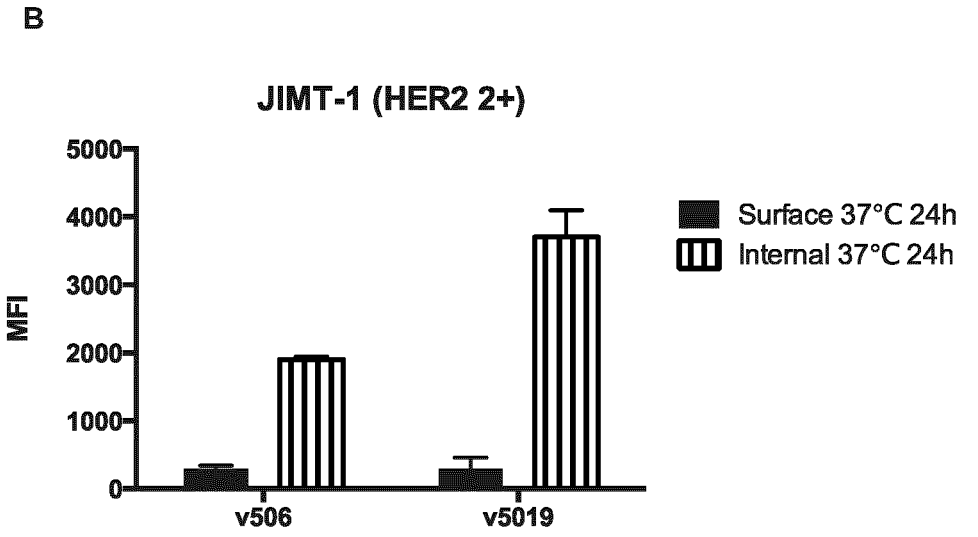

B
JIMT-1 (HER2 2+)
5000
4000
3000
2000
1000
0
MFI
v506
v5019
Surface 37°C 24h
Internal 37°C 24h

FIG. 9

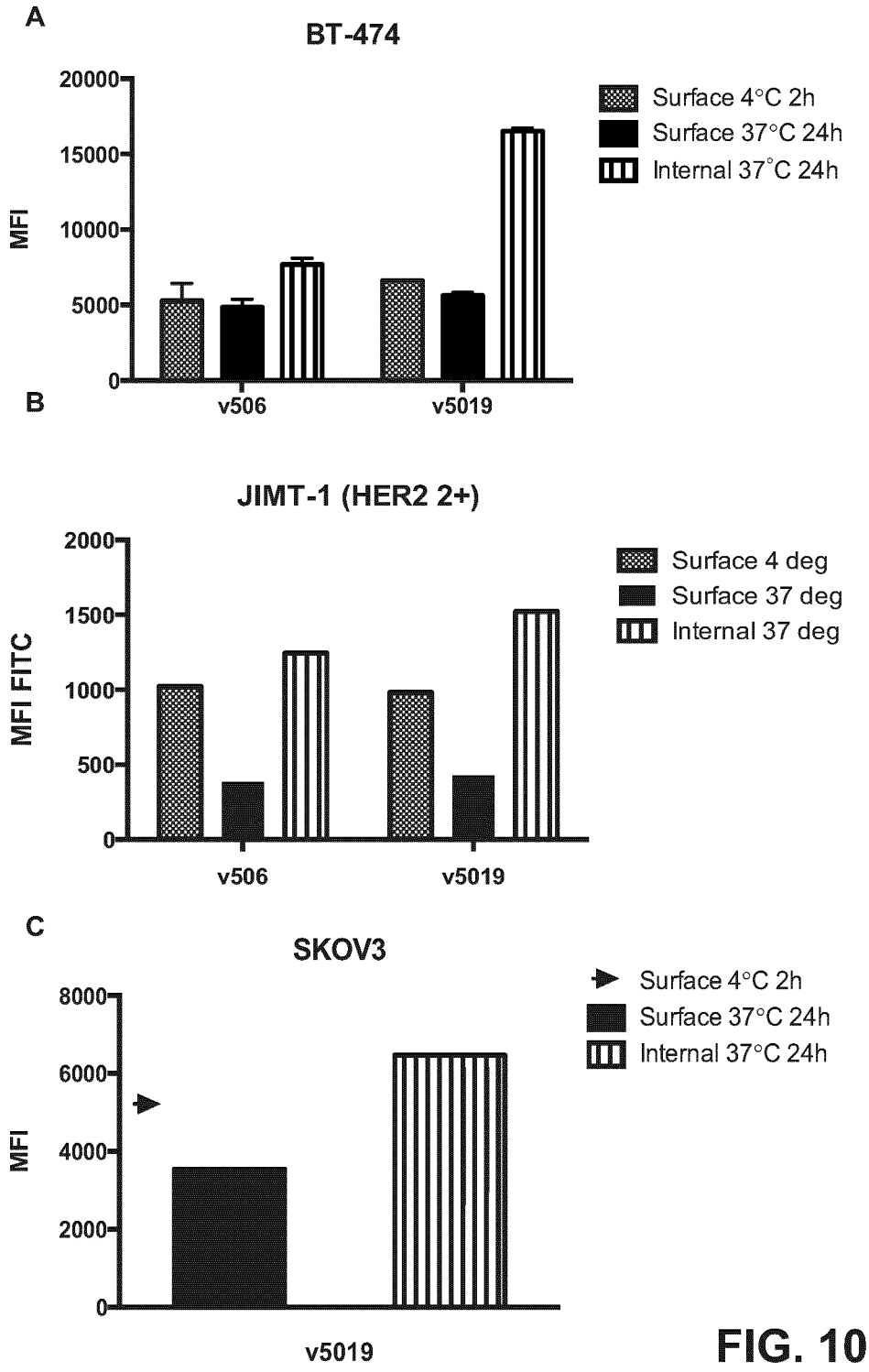

A
BT-474
20000
15000
10000
5000
0
MFI
Surface 4°C 2h
Surface 37°C 24h
Internal 37°C 24h
v506
v5019
B
JIMT-1 (HER2 2+)
2000
1500
1000
500
0
MFI FITC
Surface 4 deg
Surface 37 deg
Internal 37 deg
v506
v5019
C
SKOV3
8000
6000
4000
2000
0
MFI
Surface 4°C 2h
Surface 37°C 24h
Internal 37°C 24h
v5019

FIG. 10

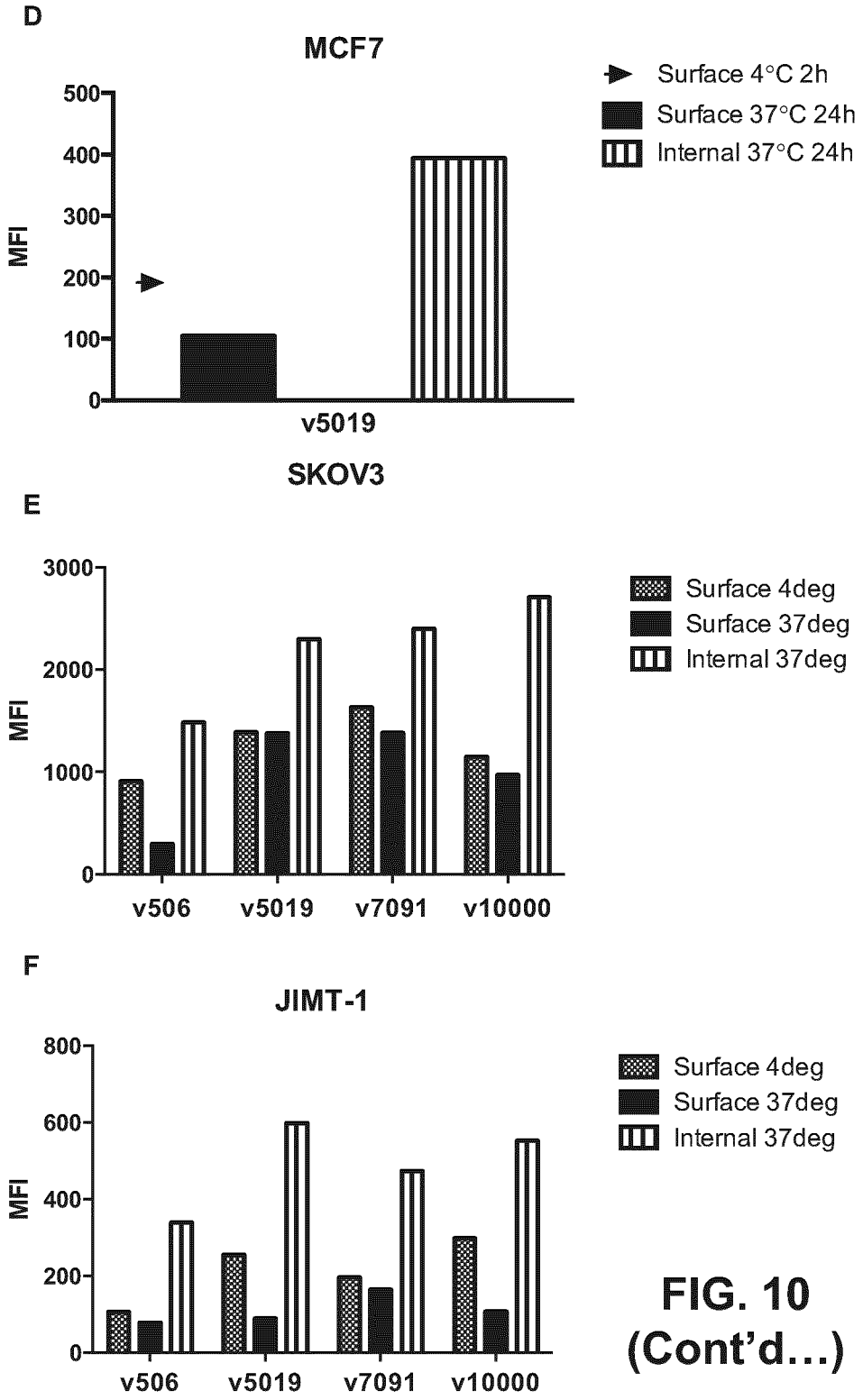
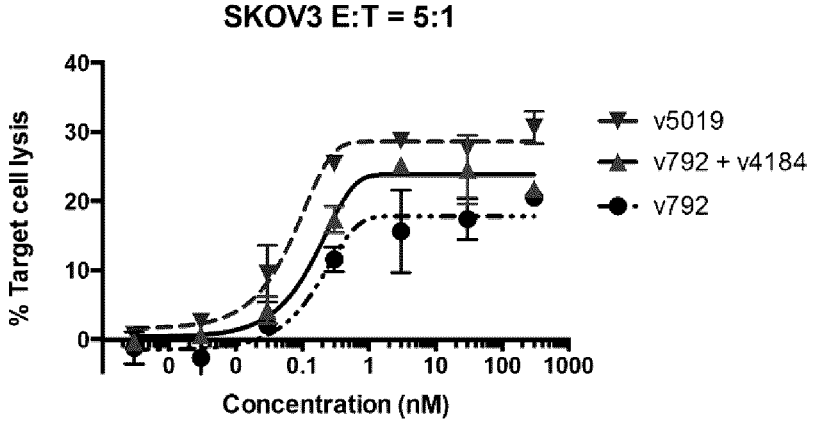
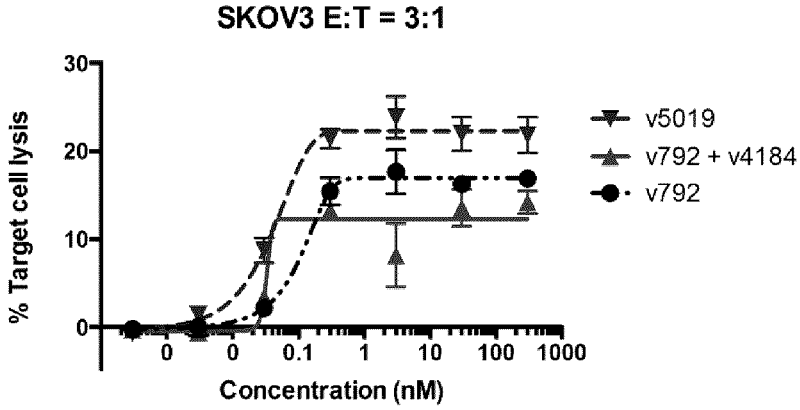

D
MCF7
Surface 4°C 2h
Surface 37°C 24h
Internal 37°C 24h
MFI
500
400
300
200
100
0
v5019
SKOV3
E
Surface 4deg
Surface 37deg
Internal 37deg
MFI
3000
2000
1000
0
v506
v5019
v7091
v10000
F
JIMT-1
Surface 4deg
Surface 37deg
Internal 37deg
MFI
800
600
400
200
0
v506
v5019
v7091
v10000

FIG. 10 (Cont'd...)

A


SKOV3 E:T = 5:1
% Target cell lysis
40
30
20
10
0
0
0
0.1
1
10
100
1000
Concentration (nM)
v5019
v792 + v4184
v792

B


SKOV3 E:T = 3:1
% Target cell lysis
30
20
10
0
0
0
0.1
1
10
100
1000
Concentration (nM)
v5019
v792 + v4184
v792

C

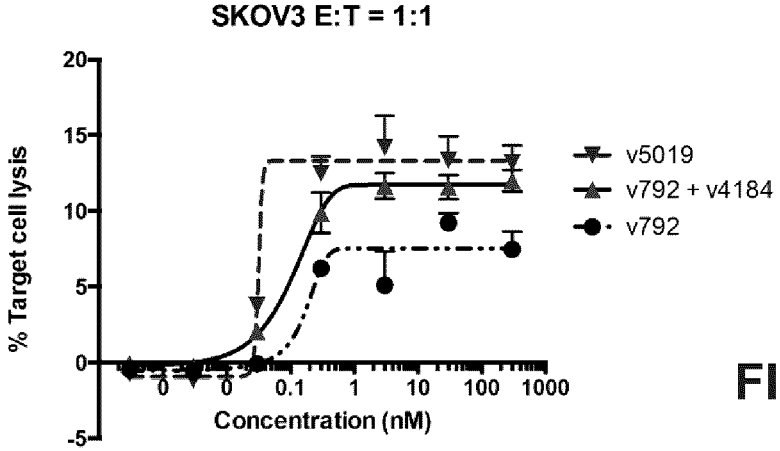

SKOV3 E:T = 1:1
% Target cell lysis
20
15
10
5
0
-5
0
0
0.1
1
10
100
1000
Concentration (nM)
v5019
v792 + v4184
v792

FIG. 11

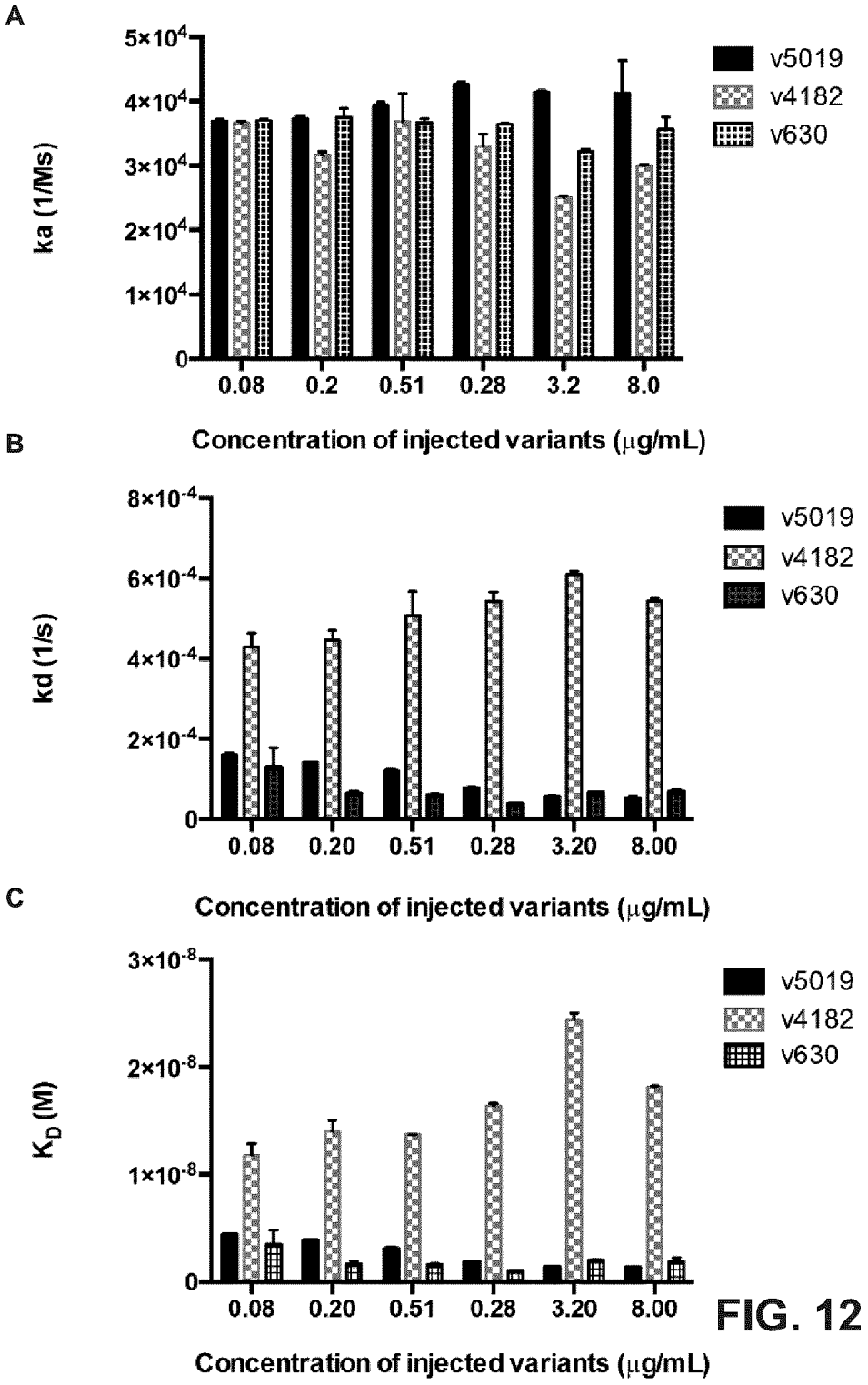

A
5×10^4
4×10^4
3×10^4
2×10^4
1×10^4
0
ka (1/Ms)
v5019
v4182
v630
0.08
0.2
0.51
0.28
3.2
8.0
Concentration of injected variants (μg/mL)
B
8×10^-4
6×10^-4
4×10^-4
2×10^-4
0
kd (1/s)
v5019
v4182
v630
0.08
0.20
0.51
0.28
3.20
8.00
Concentration of injected variants (μg/mL)
C
3×10^-8
2×10^-8
1×10^-8
0
K_D (M)
v5019
v4182
v630
0.08
0.20
0.51
0.28
3.20
8.00
Concentration of injected variants (μg/mL)

FIG. 12

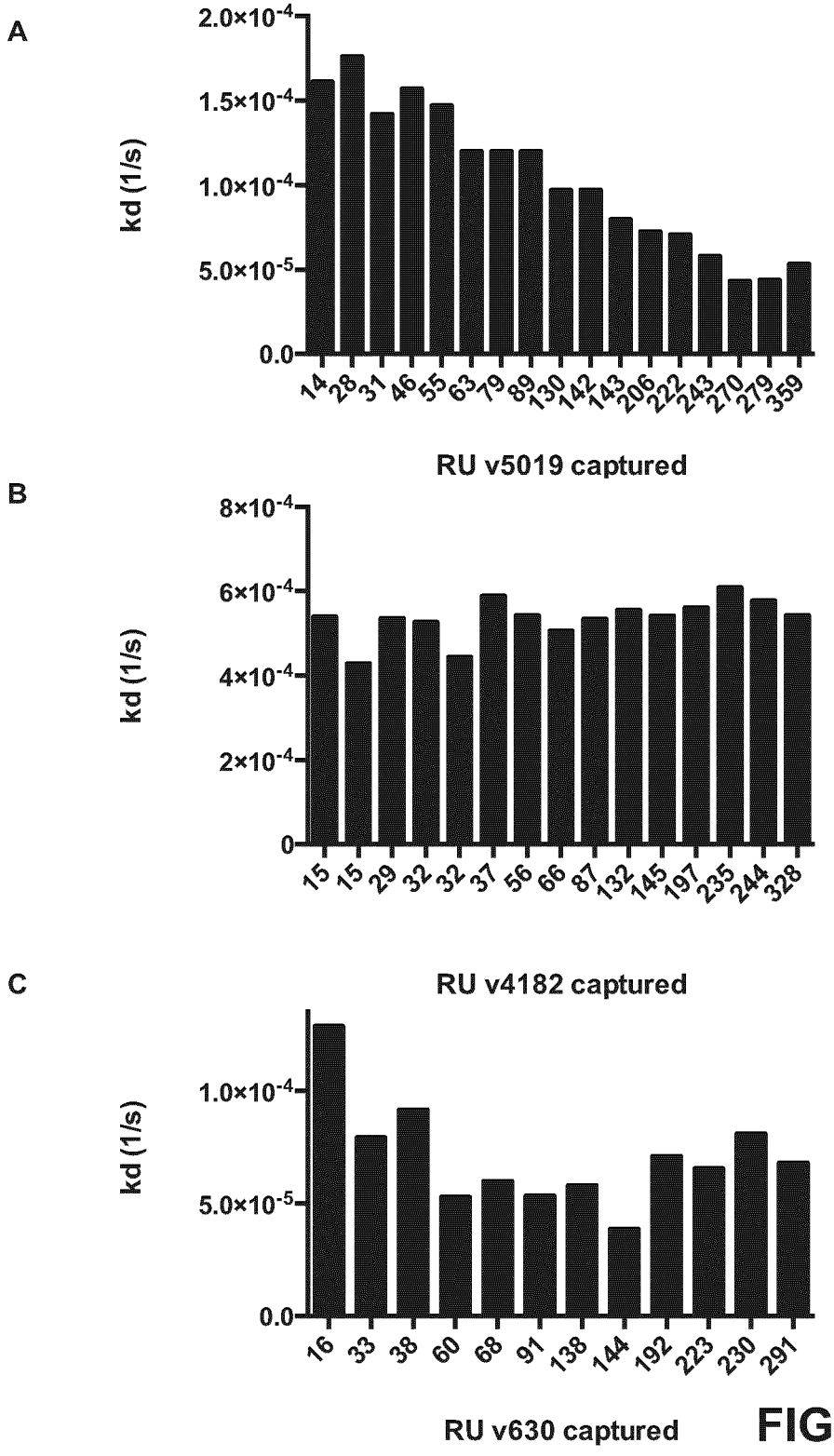
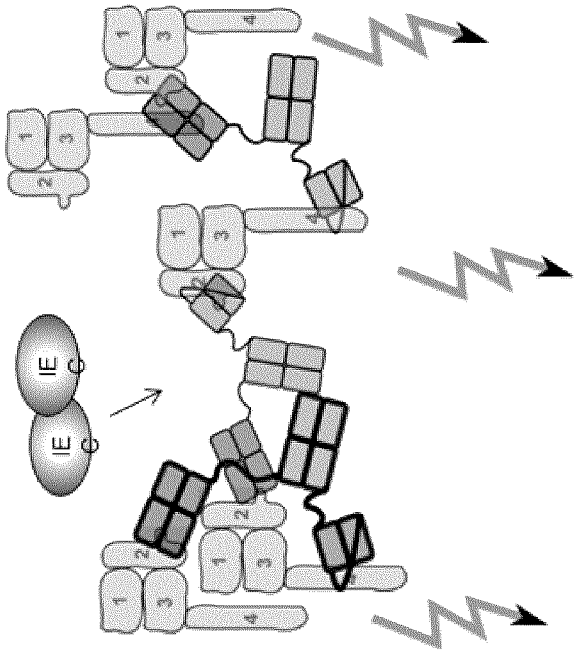

A
2.0×10-4
1.5×10-4
1.0×10-4
5.0×10-5
0.0
kd (1/s)
14 28 31 46 55 63 79 89 130 142 143 206 222 243 270 279 359
RU v5019 captured
B
8×10-4
6×10-4
4×10-4
2×10-4
0
kd (1/s)
15 15 29 32 32 37 56 66 87 132 145 197 235 244 328
RU v4182 captured
C
1.0×10-4
5.0×10-5
0.0
kd (1/s)
16 33 38 60 68 91 138 144 192 223 230 291
RU v630 captured

FIG. 13



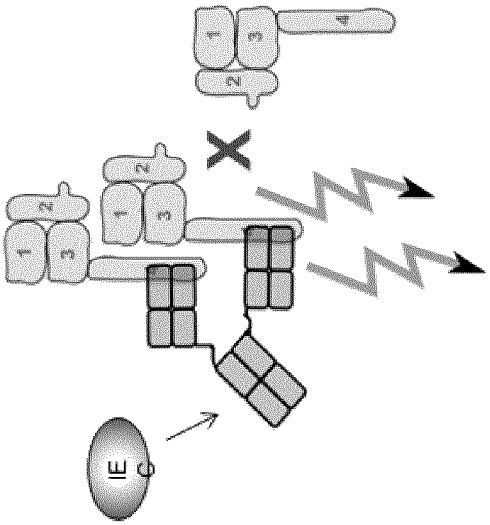


FIG. 14

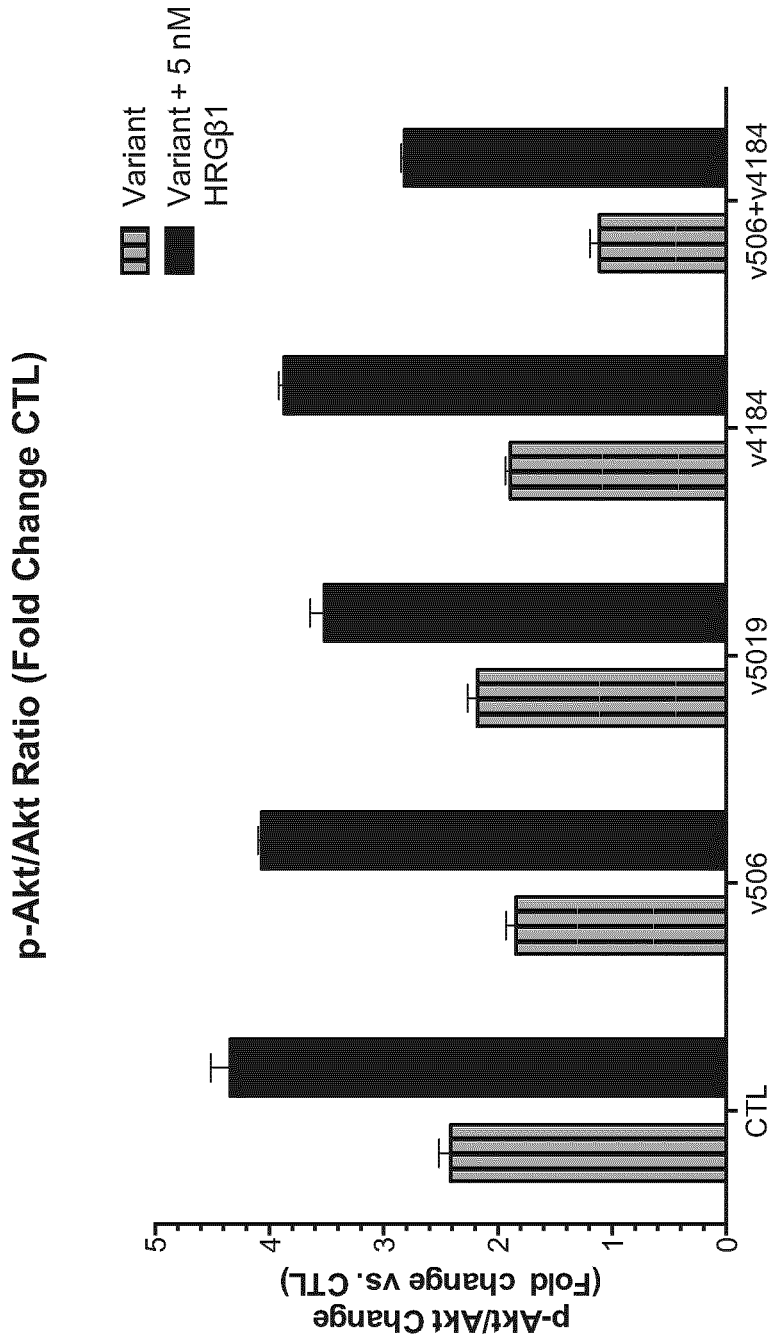

p-Akt/Akt Ratio (Fold Change CTL)
Variant
Variant + 5 nM HRGβ1
p-Akt/Akt Change (Fold change vs. CTL)
0
1
2
3
4
5
CTL
v506
v5019
v4184
v506+v4184

FIG. 15

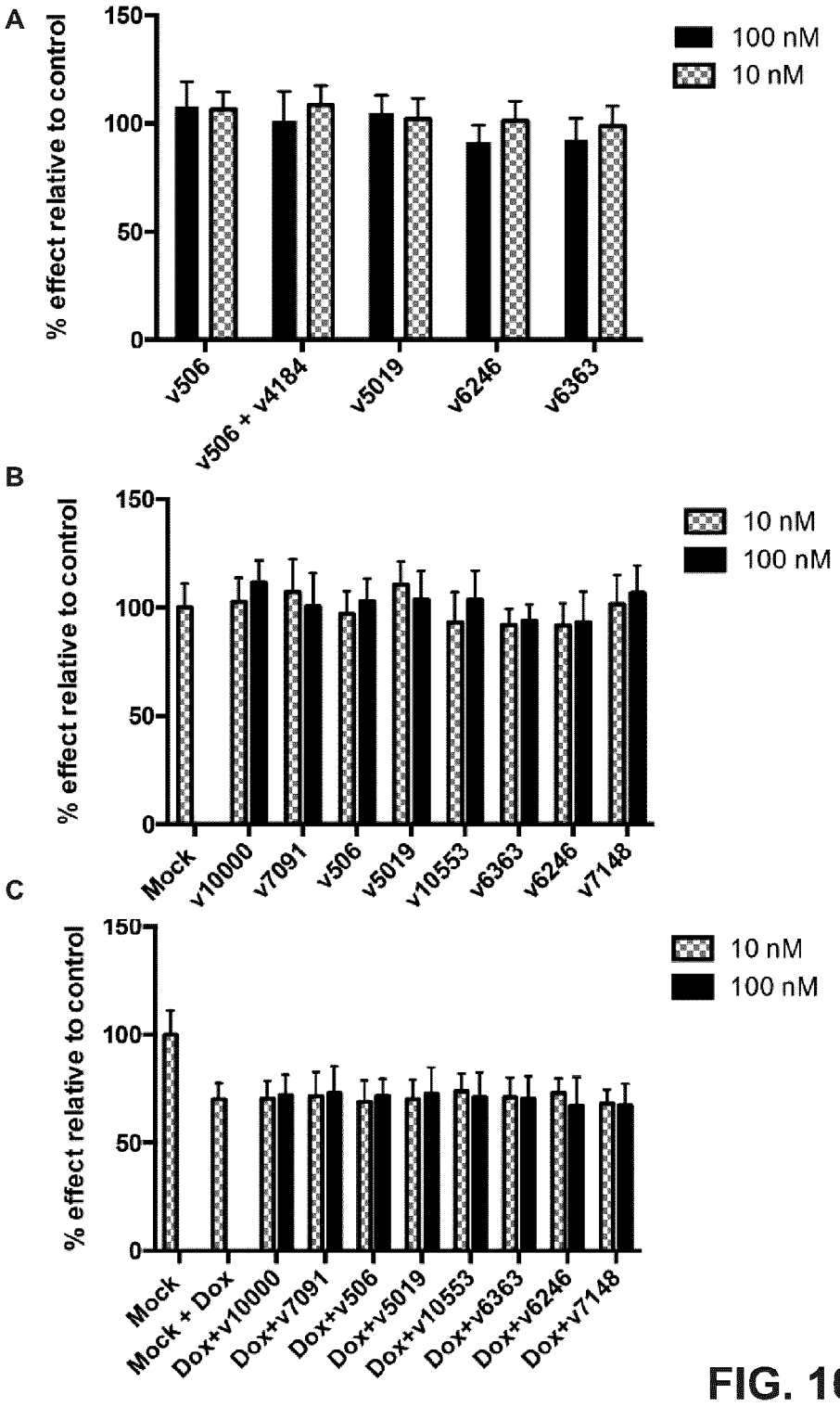
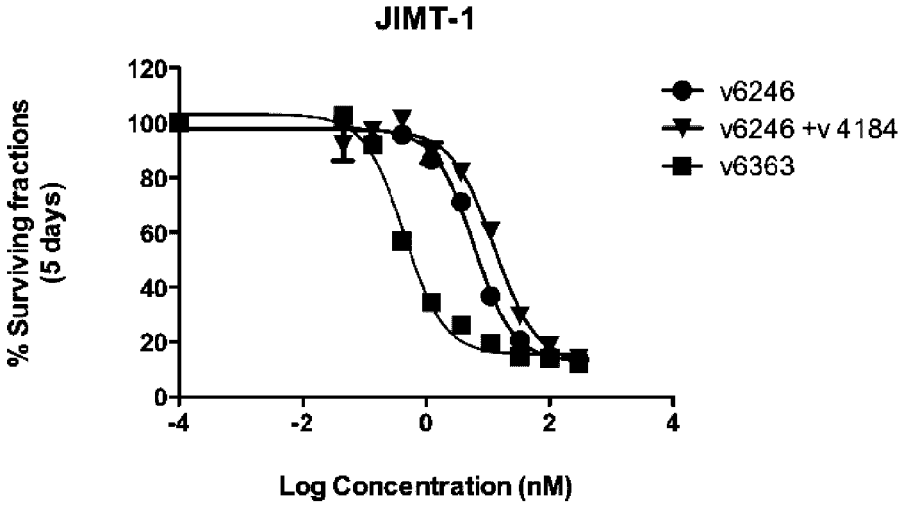

A
% effect relative to control
150
100
50
0
100 nM
10 nM
v506
v506 + v4184
v5019
v6246
v6363
B
% effect relative to control
150
100
50
0
10 nM
100 nM
Mock
v10000
v7091
v506
v5019
v10553
v6363
v6246
v7148
C
% effect relative to control
150
100
50
0
10 nM
100 nM
Mock
Mock + Dox
Dox+v10000
Dox+v7091
Dox+v506
Dox+v5019
Dox+v10553
Dox+v6363
Dox+v6246
Dox+v7148

FIG. 16

A


JIMT-1
% Surviving fractions (5 days)
120
100
80
60
40
20
0
-4
-2
0
2
4
Log Concentration (nM)
v6246
v6246 +v 4184
v6363

B

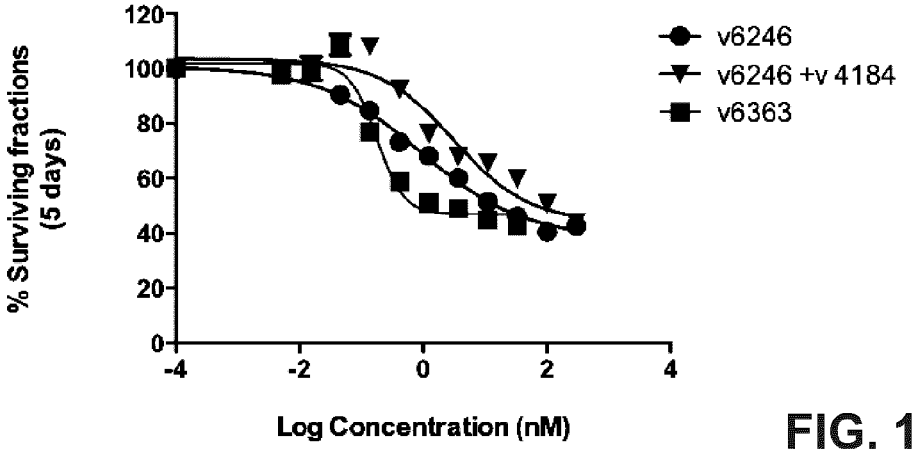
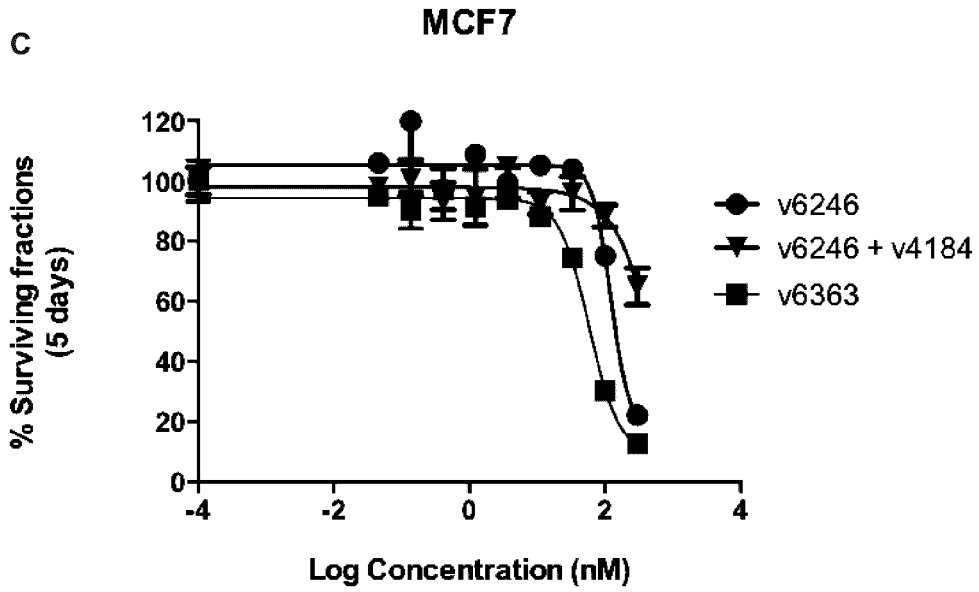

SKOV3
% Surviving fractions (5 days)
120
100
80
60
40
20
0
-4
-2
0
2
4
Log Concentration (nM)
v6246
v6246 +v 4184
v6363

FIG. 17

C



D

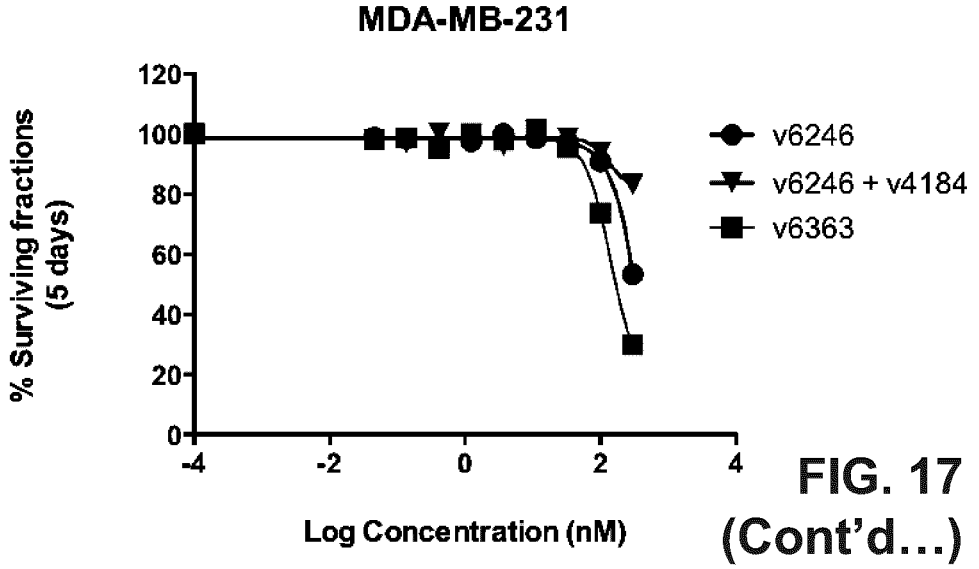
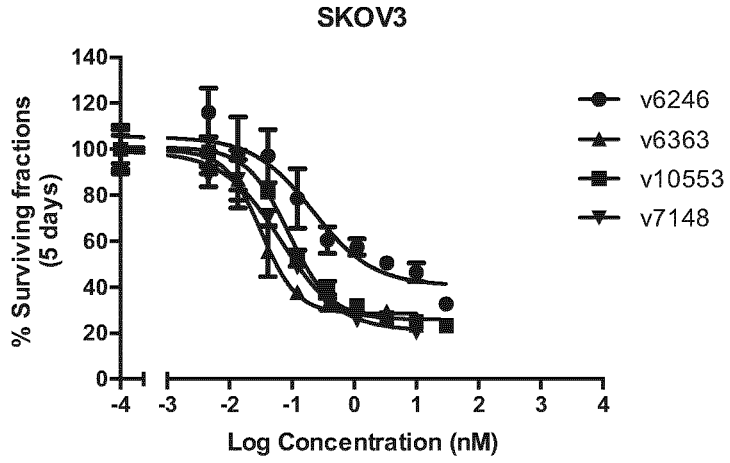
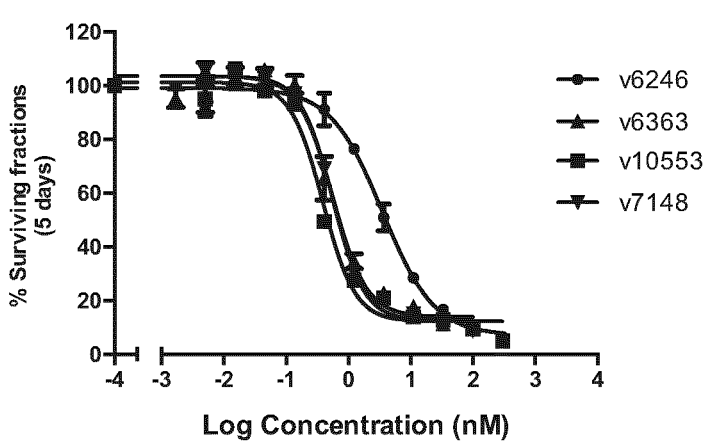


FIG. 17 (Cont'd...)

E



F



G

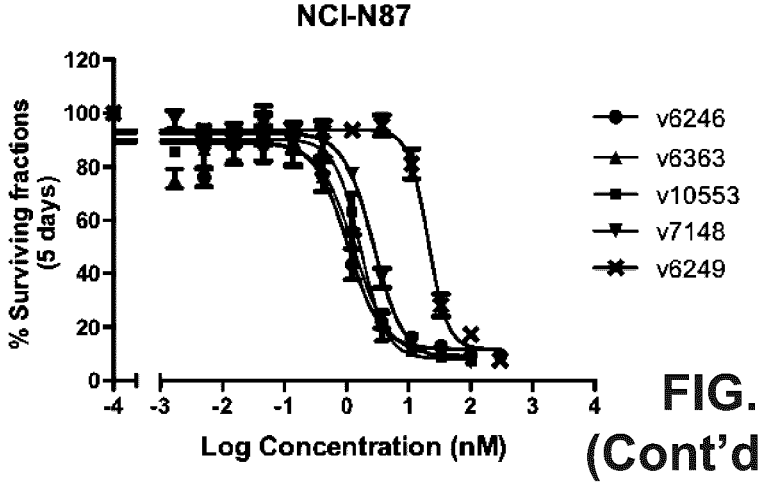


FIG. 17 (Cont'd...)

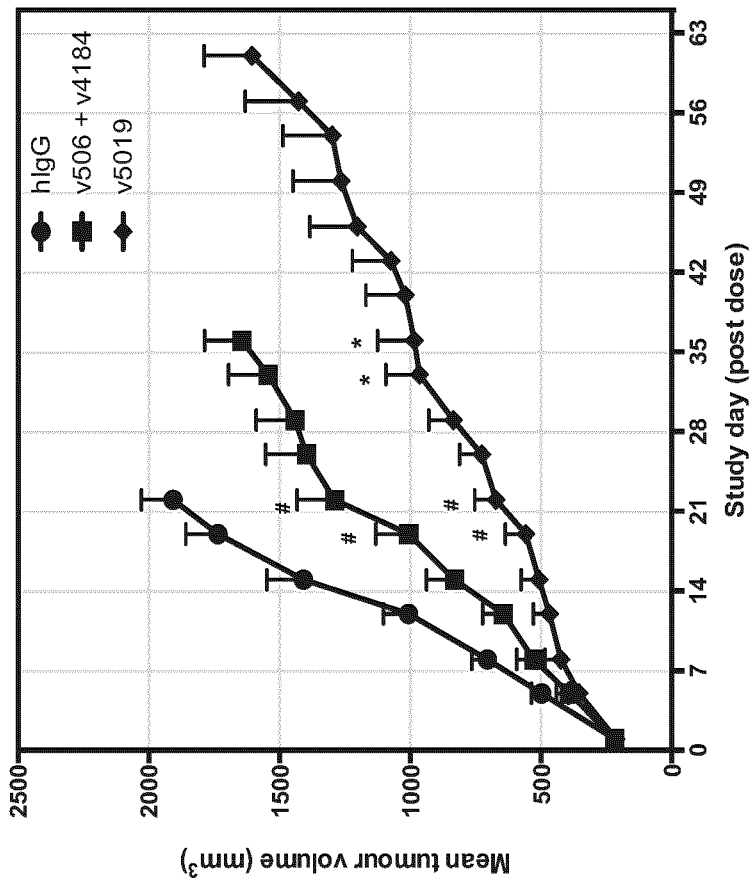

hIgG
v506 + v4184
v5019
Mean tumour volume (mm³)
2500
2000
1500
1000
500
0
0
7
14
21
28
35
42
49
56
63
Study day (post dose)
#
*
ANOVA
*, p<0.05 vs v506
#, p<0.05 vs IgG

FIG. 18A

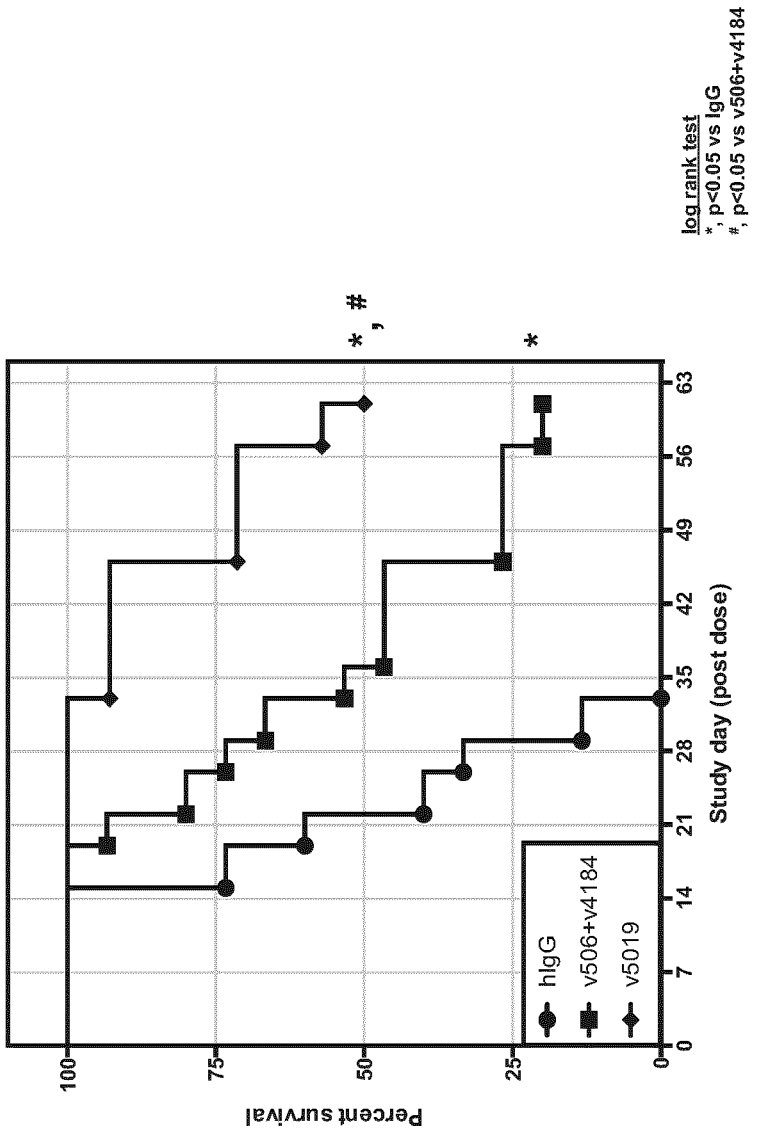

log rank test
*, p<0.05 vs IgG
#, p<0.05 vs v506+v4184
*, #
*
Percent survival
100
75
50
25
0
0
7
14
21
28
35
42
49
56
63
Study day (post dose)
hIgG
v506+v4184
v5019

FIG. 18B

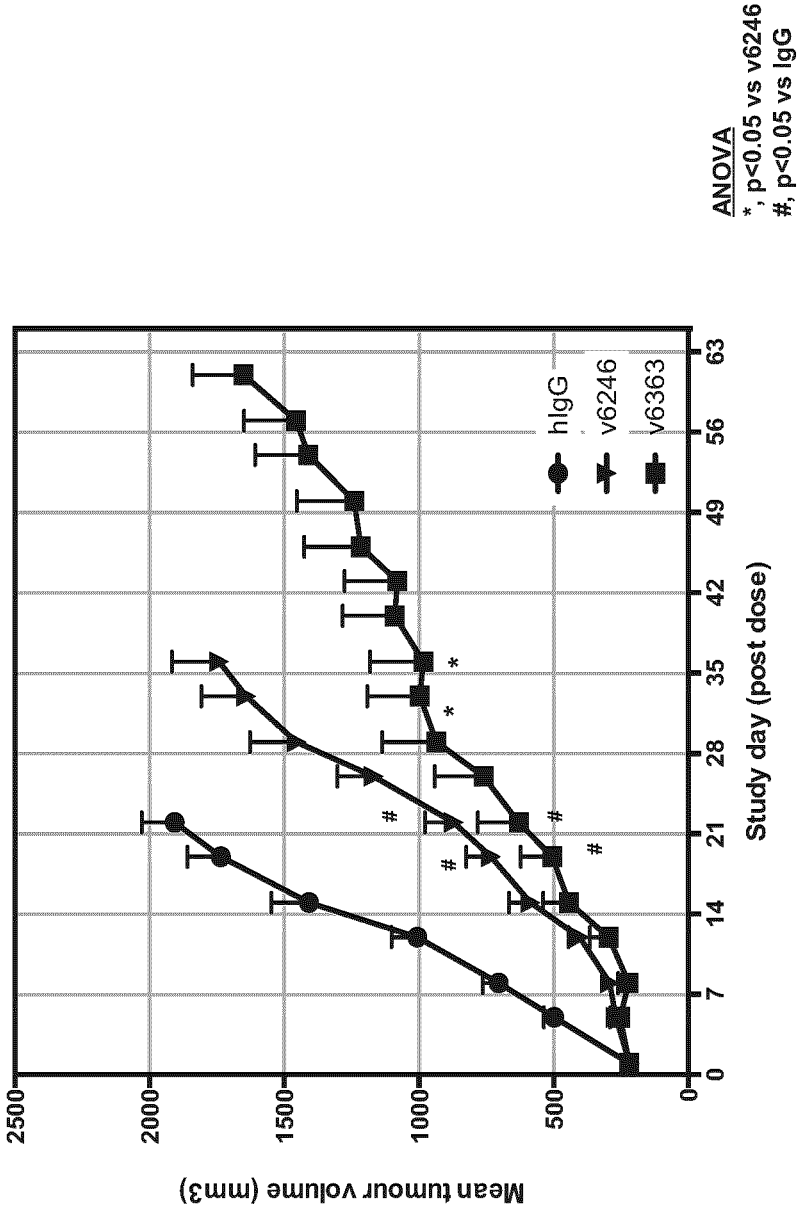

ANOVA
*, p<0.05 vs v6246
#, p<0.05 vs IgG
hIgG
v6246
v6363
Mean tumour volume (mm3)
Study day (post dose)
0
500
1000
1500
2000
2500
0
7
14
21
28
35
42
49
56
63
*
#

FIG. 19A

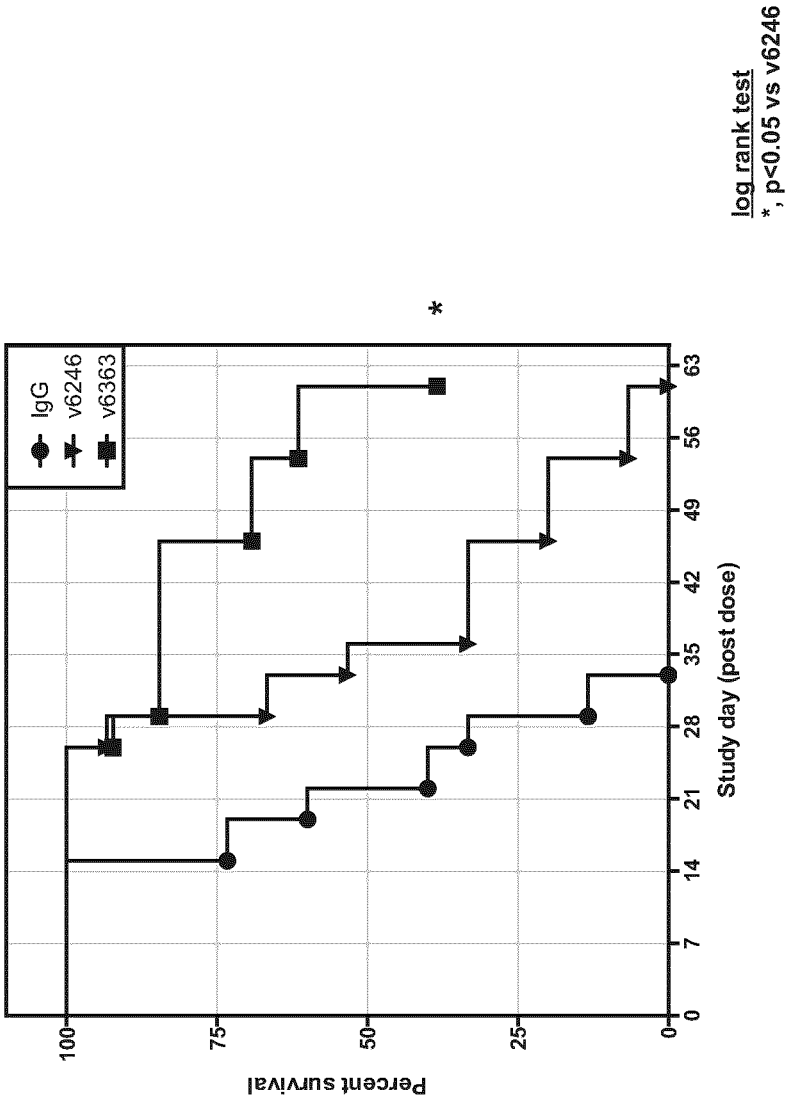

log rank test
*, p<0.05 vs v6246
*
IgG
v6246
v6363
Percent survival
100
75
50
25
0
0
7
14
21
28
35
42
49
56
63
Study day (post dose)

FIG. 19B

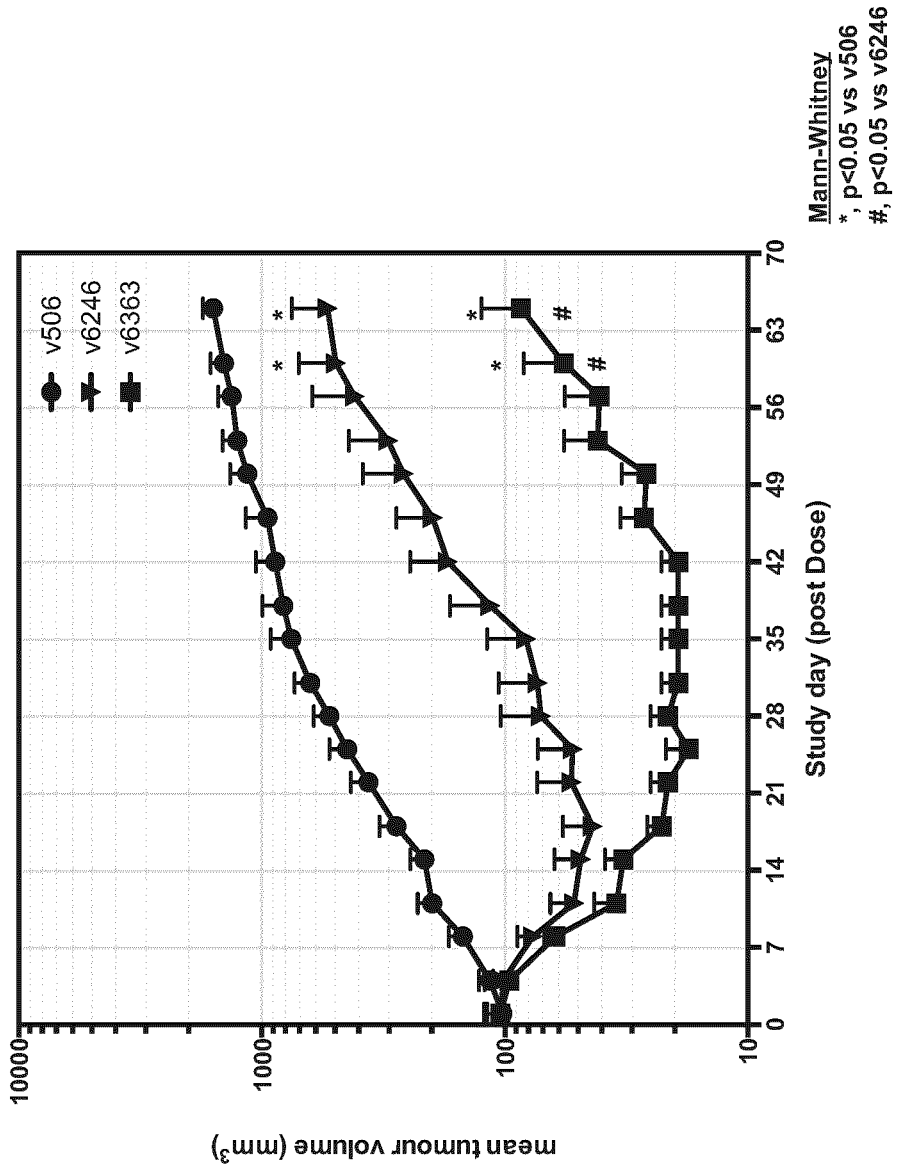

v506
v6246
v6363
10000
1000
100
10
0
7
14
21
28
35
42
49
56
63
70
Study day (post Dose)
mean tumour volume (mm3)
*
#
Mann-Whitney
*, p<0.05 vs v506
#, p<0.05 vs v6246

FIG. 20

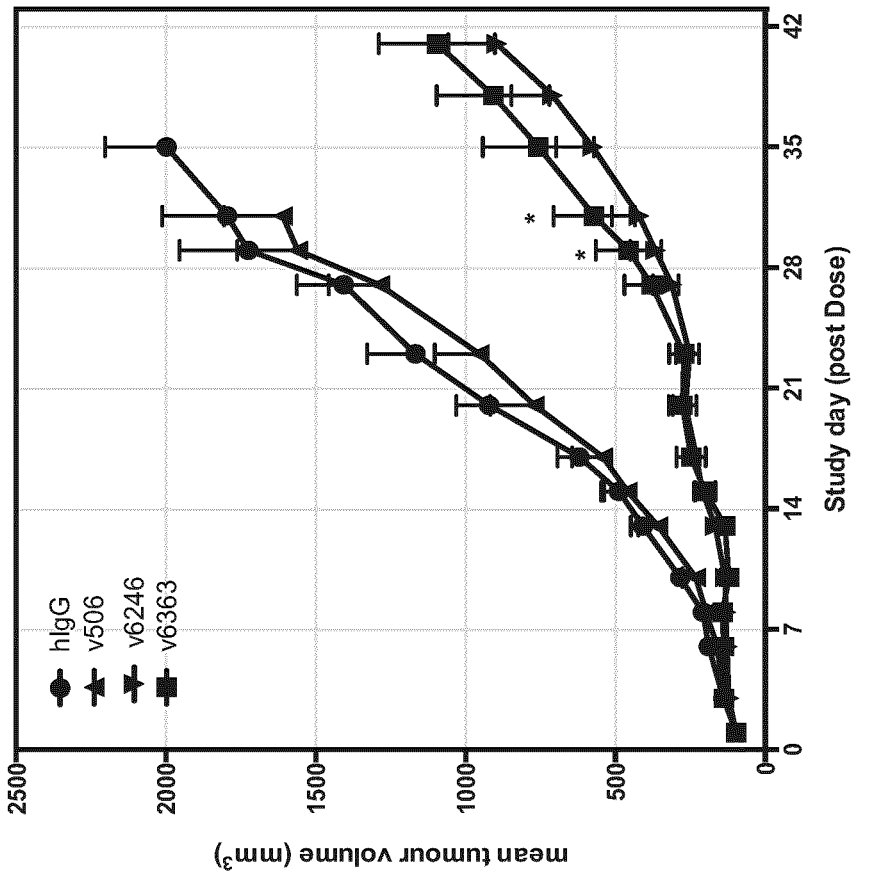

mean tumour volume (mm³)
2500
2000
1500
1000
500
0
0
7
14
21
28
35
42
Study day (post Dose)
hIgG
v506
v6246
v6363
*
*
Kruskal-Wallis
*, p<0.05 vs v506

FIG. 21

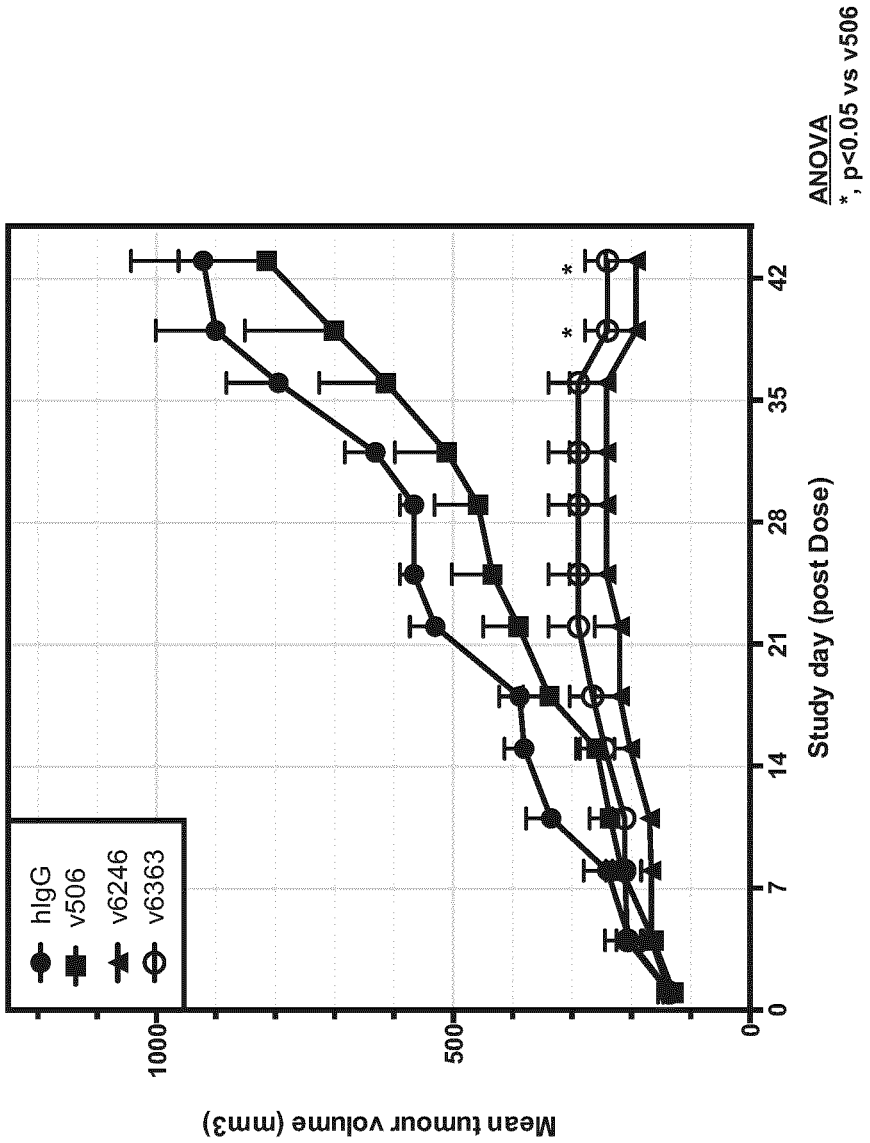

ANOVA
*, p<0.05 vs v506
hIgG
v506
v6246
v6363
Mean tumour volume (mm3)
1000
500
0
0
7
14
21
28
35
42
Study day (post Dose)
*
*

FIG. 22

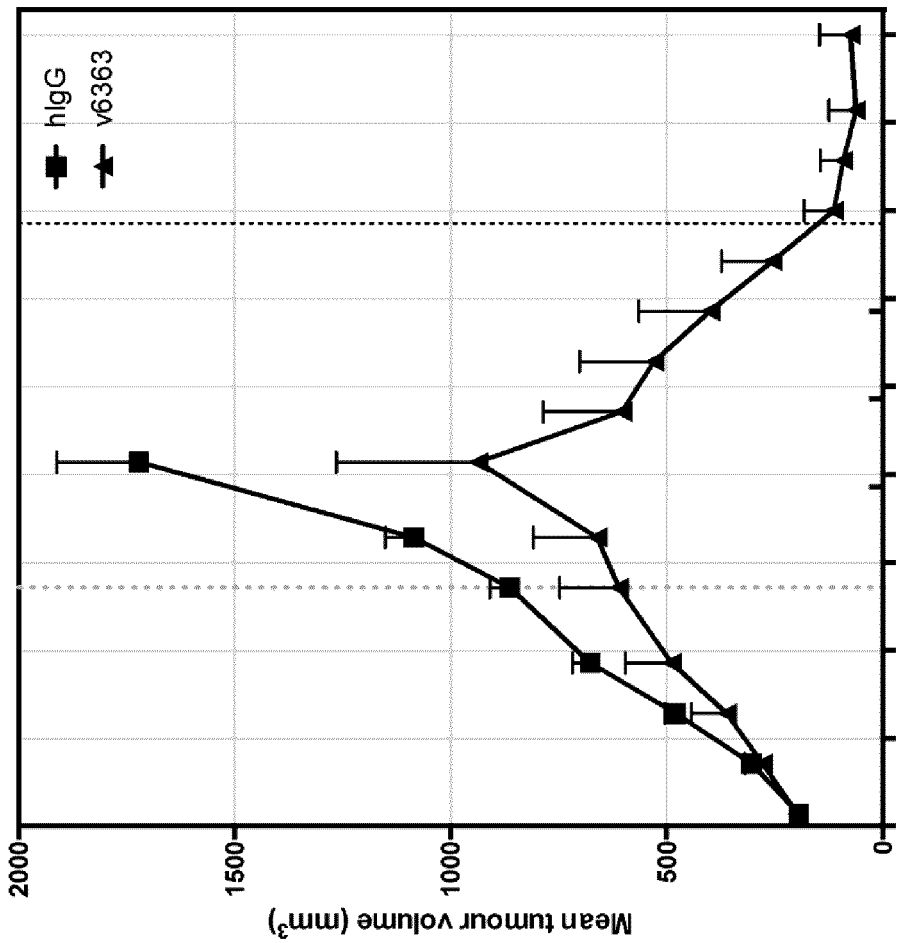

hIgG
v6363
Mean tumour volume (mm³)
2000
1500
1000
500
0
0
7
14
21
28
35
42
49
56
63
Study day (post Dose)

FIG. 23

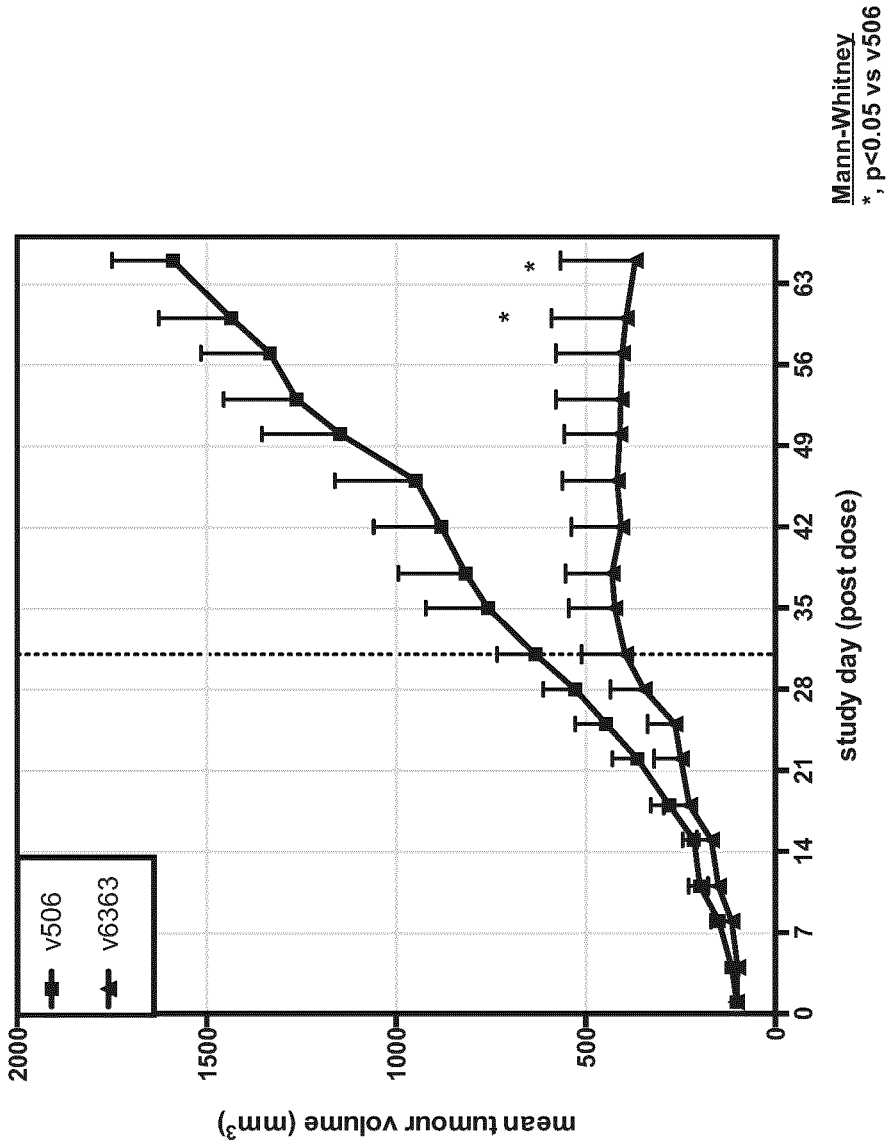

Mann-Whitney
*, p<0.05 vs v506
v506
v6363
mean tumour volume (mm³)
2000
1500
1000
500
0
0
7
14
21
28
35
42
49
56
63
study day (post dose)
*
*

FIG. 24

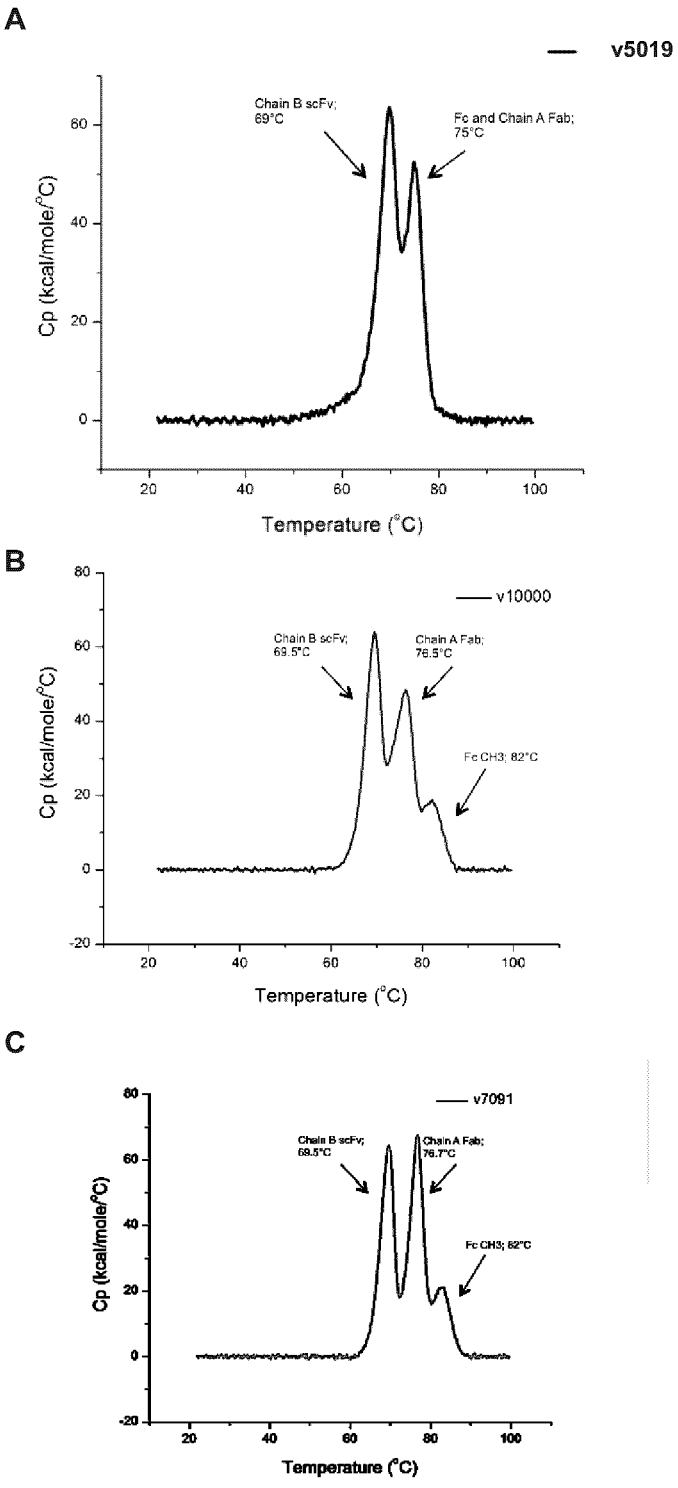

A
v5019
Chain B scFv; 69°C
Fc and Chain A Fab; 75°C
Cp (kcal/mole/°C)
Temperature (°C)
B
v10000
Chain B scFv; 69.5°C
Chain A Fab; 76.5°C
Fc CH3; 82°C
Cp (kcal/mole/°C)
Temperature (°C)
C
v7091
Chain B scFv; 69.5°C
Chain A Fab; 76.7°C
Fc CH3; 82°C
Cp (kcal/mole/°C)
Temperature (°C)

FIG. 25

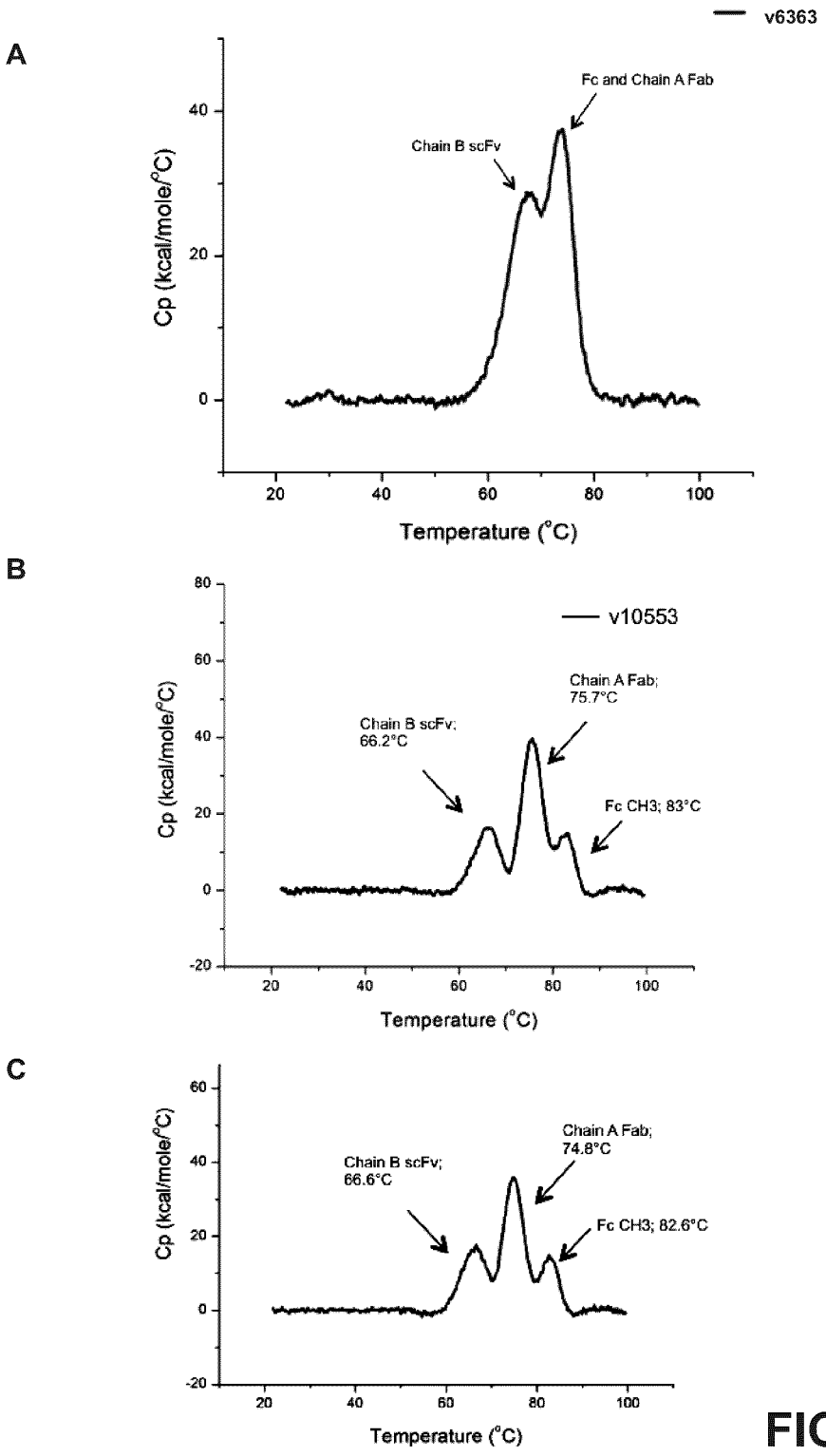
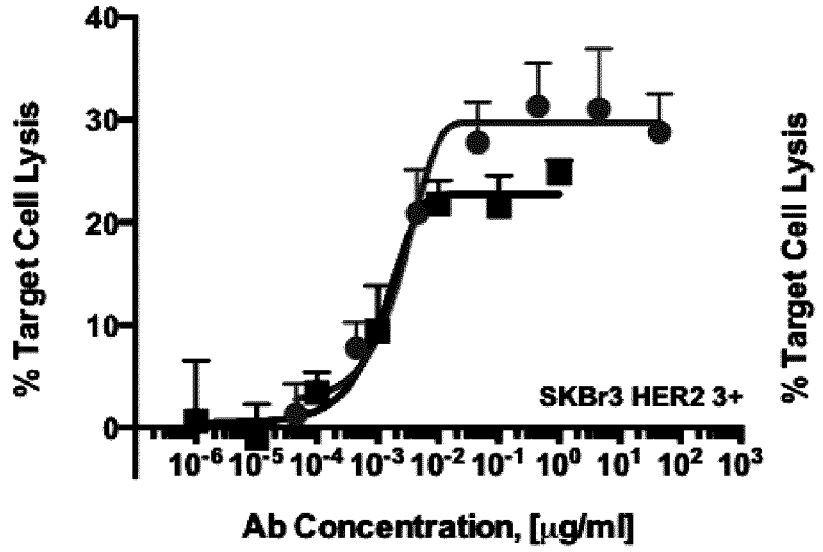

A
v6363
Fc and Chain A Fab
Chain B scFv
Cp (kcal/mole/°C)
Temperature (°C)
B
v10553
Chain A Fab;
75.7°C
Chain B scFv;
66.2°C
Fc CH3; 83°C
Cp (kcal/mole/°C)
Temperature (°C)
C
Chain A Fab;
74.8°C
Chain B scFv;
66.6°C
Fc CH3; 82.6°C
Cp (kcal/mole/°C)
Temperature (°C)

FIG. 26

A


40
30
20
10
0
% Target Cell Lysis
% Target Cell Lysis
SKBr3 HER2 3+
10-6 10-5 10-4 10-3 10-2 10-1 100 101 102 103
Ab Concentration, [μg/ml]

B

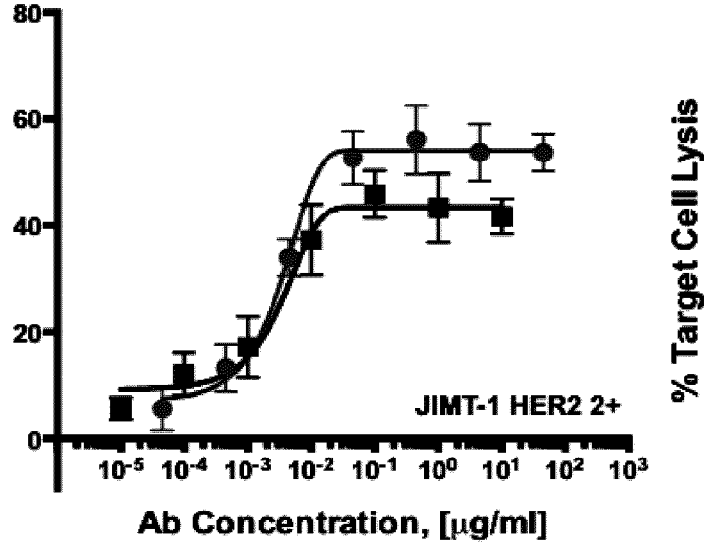
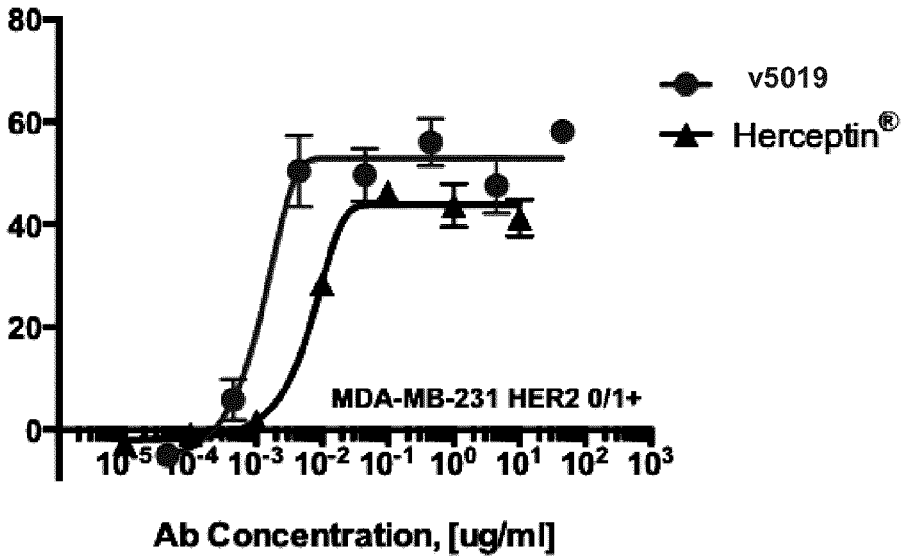

80
60
40
20
0
% Target Cell Lysis
JIMT-1 HER2 2+
10-5 10-4 10-3 10-2 10-1 100 101 102 103
Ab Concentration, [μg/ml]

FIG. 27

C



D

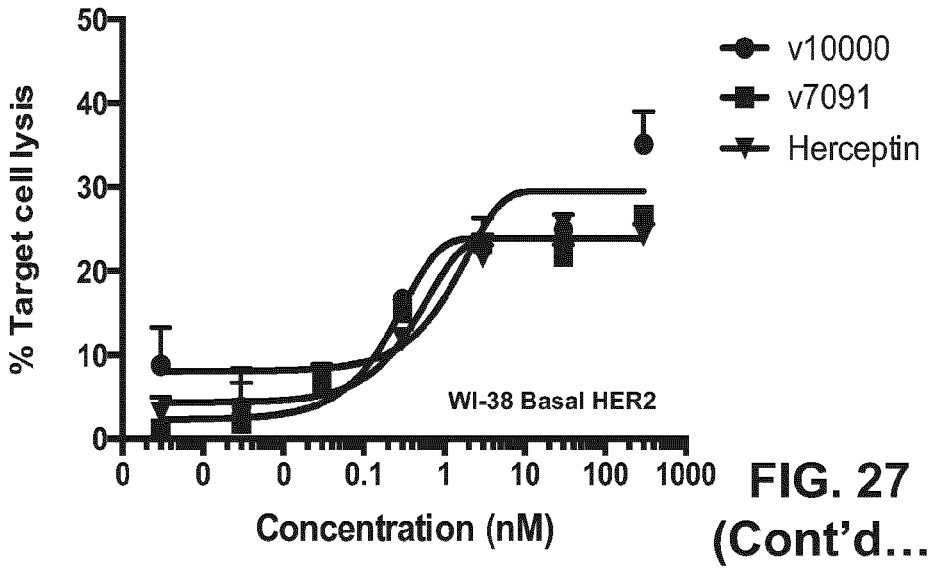
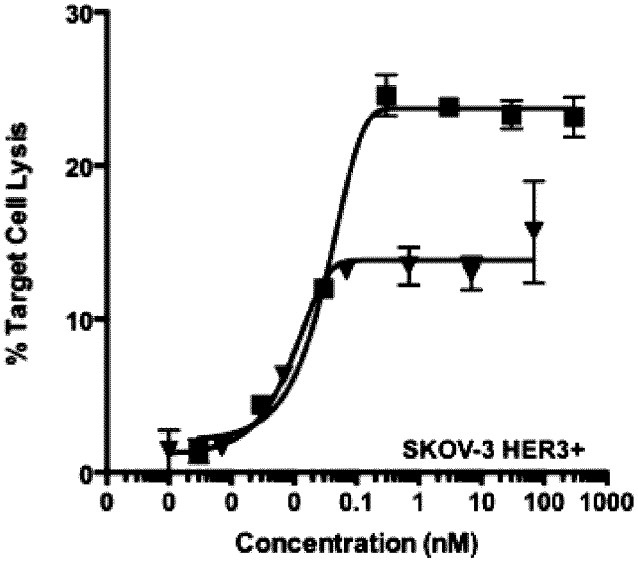


FIG. 27 (Cont'd...)

A


% Target Cell Lysis
30
20
10
0
SKOV-3 HER3+
0 0 0 0 0.1 1 10 100 1000
Concentration (nM)

B

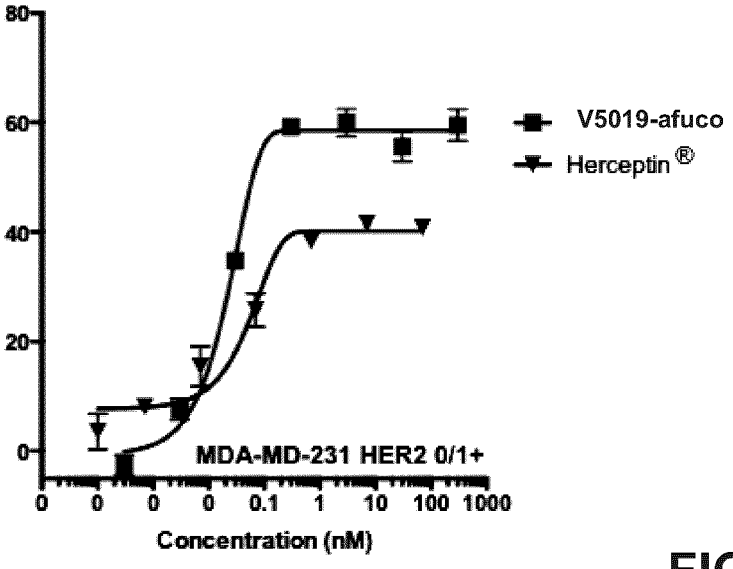

80
60
40
20
0
MDA-MD-231 HER2 0/1+
0 0 0 0 0.1 1 10 100 1000
Concentration (nM)
V5019-afuco
Herceptin®

FIG. 28

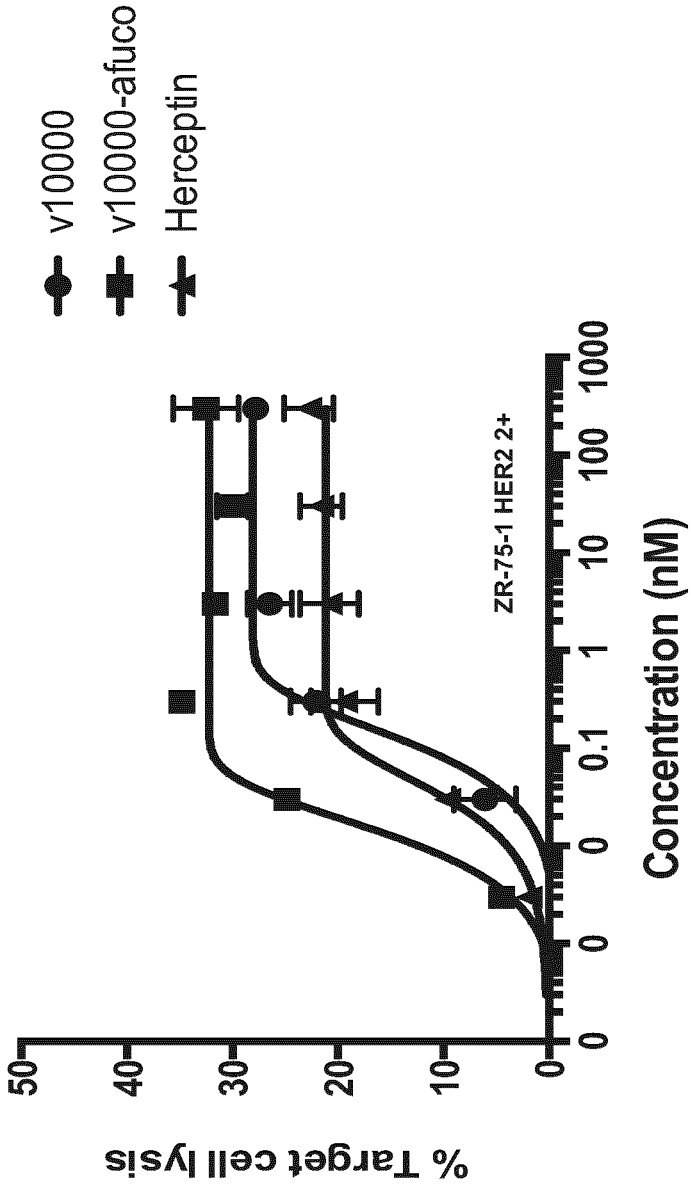

v10000
v10000-afuco
Herceptin
ZR-75-1 HER2 2+
% Target cell lysis
0
10
20
30
40
50
0
0
0
0.1
1
10
100
1000
Concentration (nM)

FIG. 28C

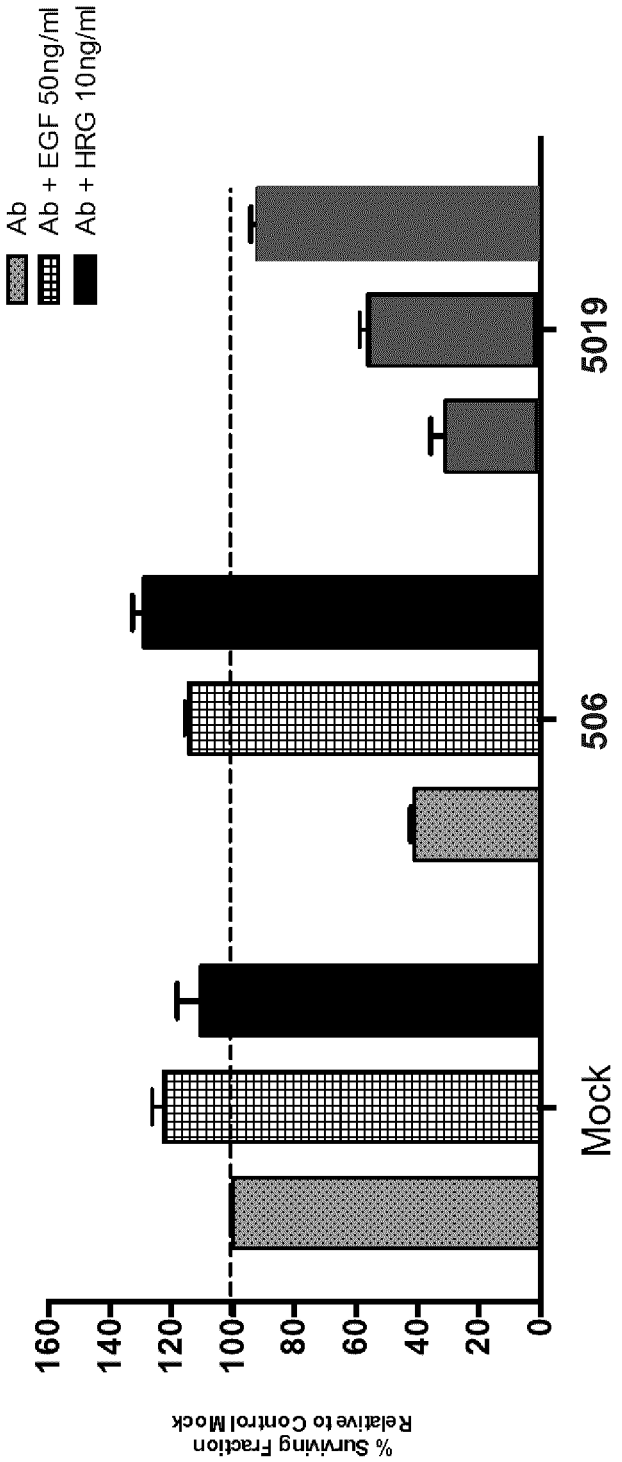

Ab
Ab + EGF 50ng/ml
Ab + HRG 10ng/ml
% Surviving Fraction
Relative to Control Mock
160
140
120
100
80
60
40
20
0
Mock
506
5019

FIG. 29

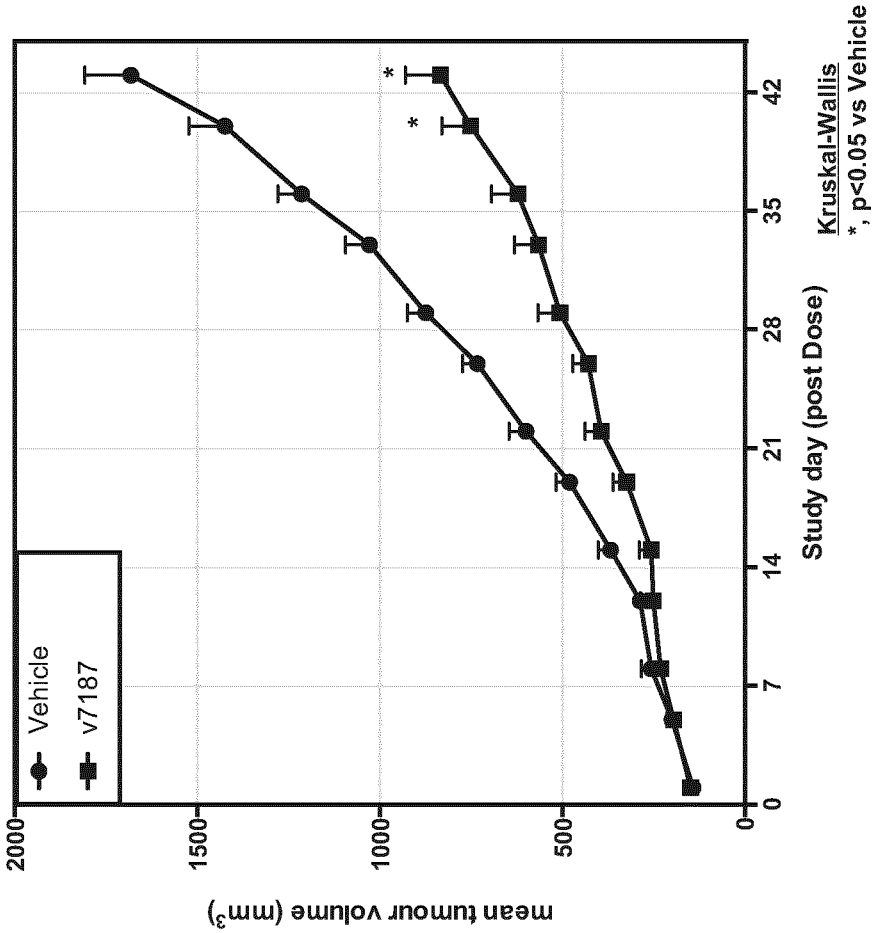
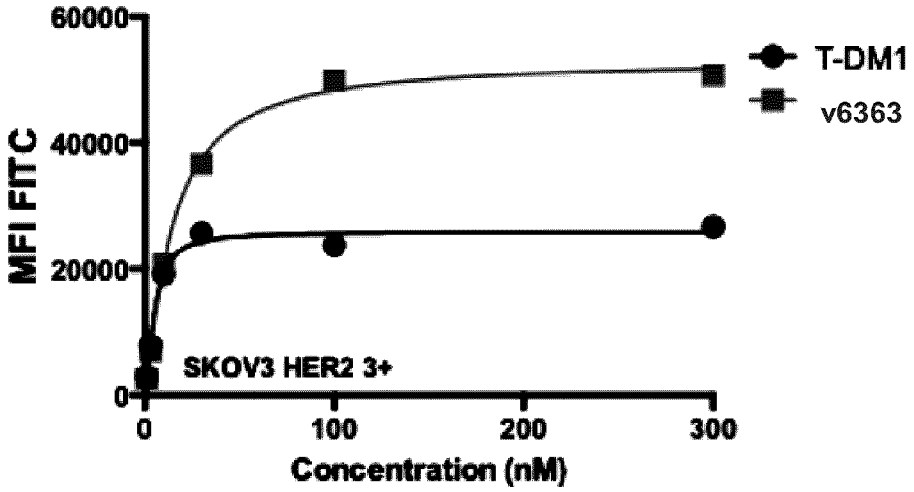

mean tumour volume (mm³)
2000
1500
1000
500
0
Vehicle
v7187
0
7
14
21
28
35
42
Study day (post Dose)
Kruskal-Wallis
*, p<0.05 vs Vehicle
*
*

FIG. 30

A


60000
40000
20000
0
MFI FITC
SKOV3 HER2 3+
0
100
200
300
Concentration (nM)
T-DM1
v6363

B

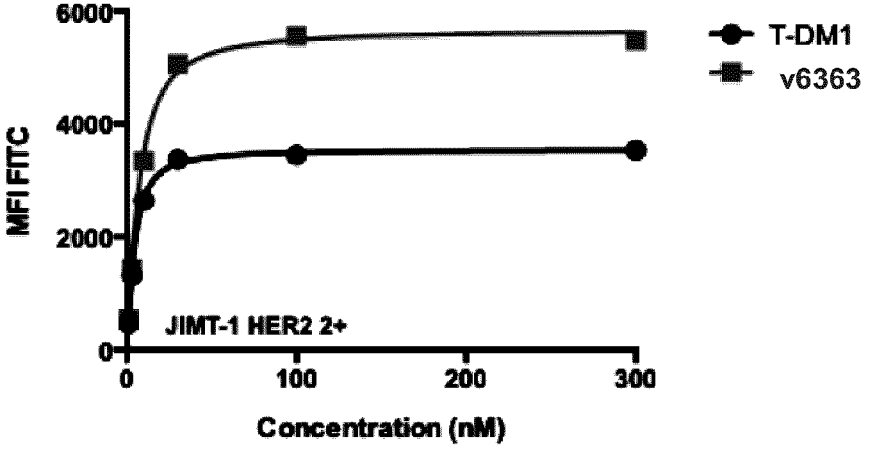
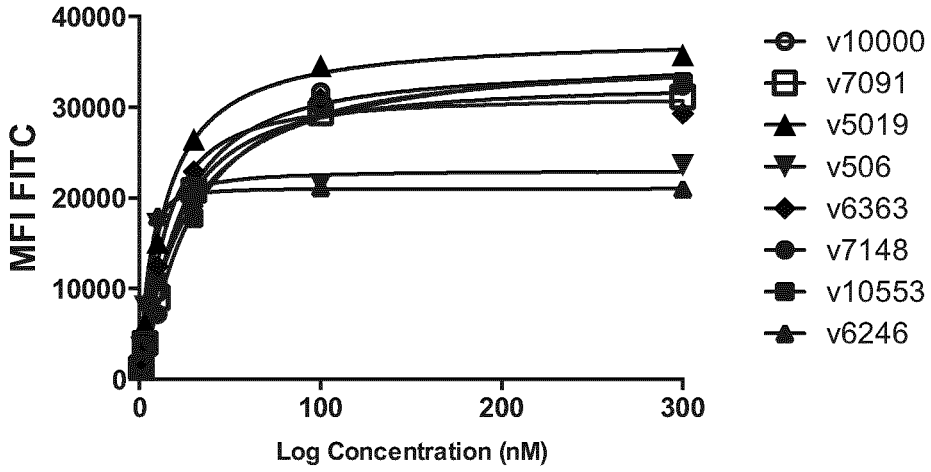

6000
4000
2000
0
MFI FITC
JIMT-1 HER2 2+
0
100
200
300
Concentration (nM)
T-DM1
v6363

FIG. 31

C



D

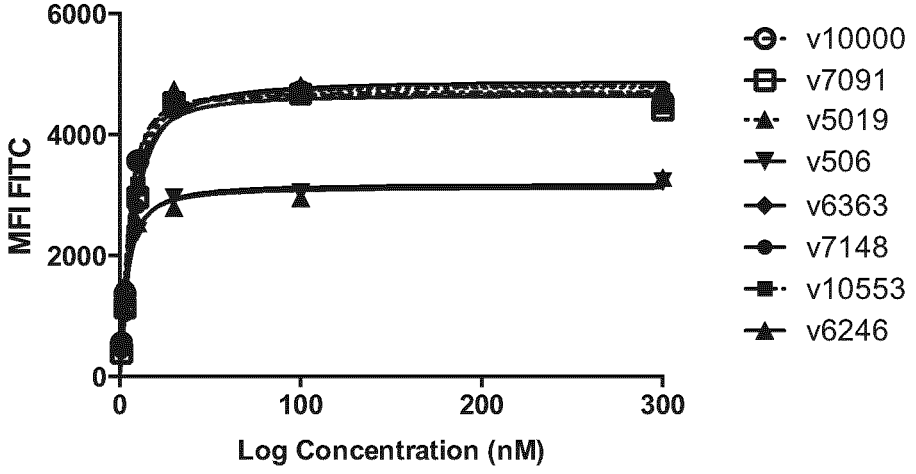


FIG. 31 (Cont'd...)

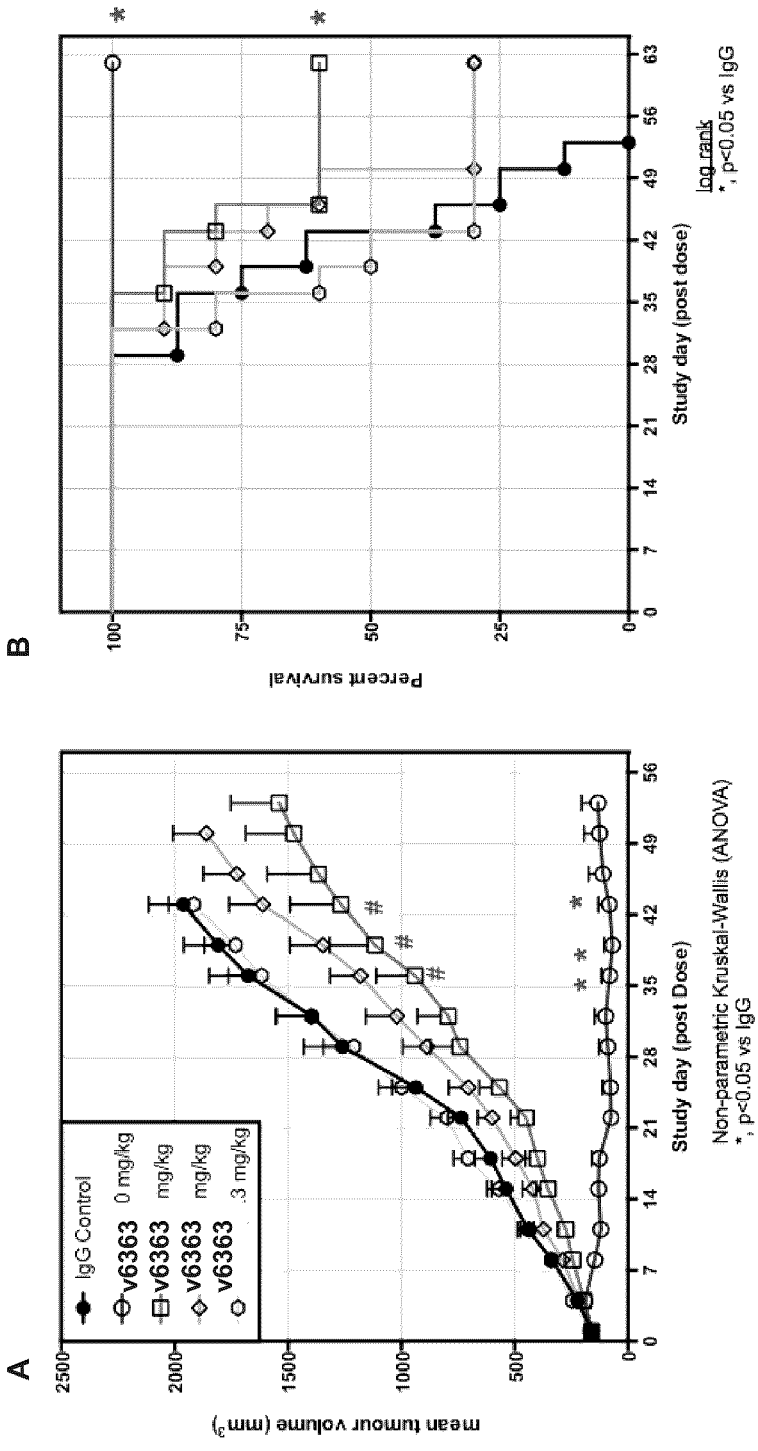

A
mean tumour volume (mm³)
2500
2000
1500
1000
500
0
0 7 14 21 28 35 42 49 56
Study day (post Dose)
IgG Control
v6363 0 mg/kg
v6363 mg/kg
v6363 mg/kg
v6363 .3 mg/kg
Non-parametric Kruskal-Wallis (ANOVA)
*, p<0.05 vs IgG
Non-parametric Mann-Whitney (T-test)
#, p<0.05 vs IgG
B
Percent survival
100
75
50
25
0
0 7 14 21 28 35 42 49 56 63
Study day (post dose)
Log rank
*, p<0.05 vs IgG

FIG. 32

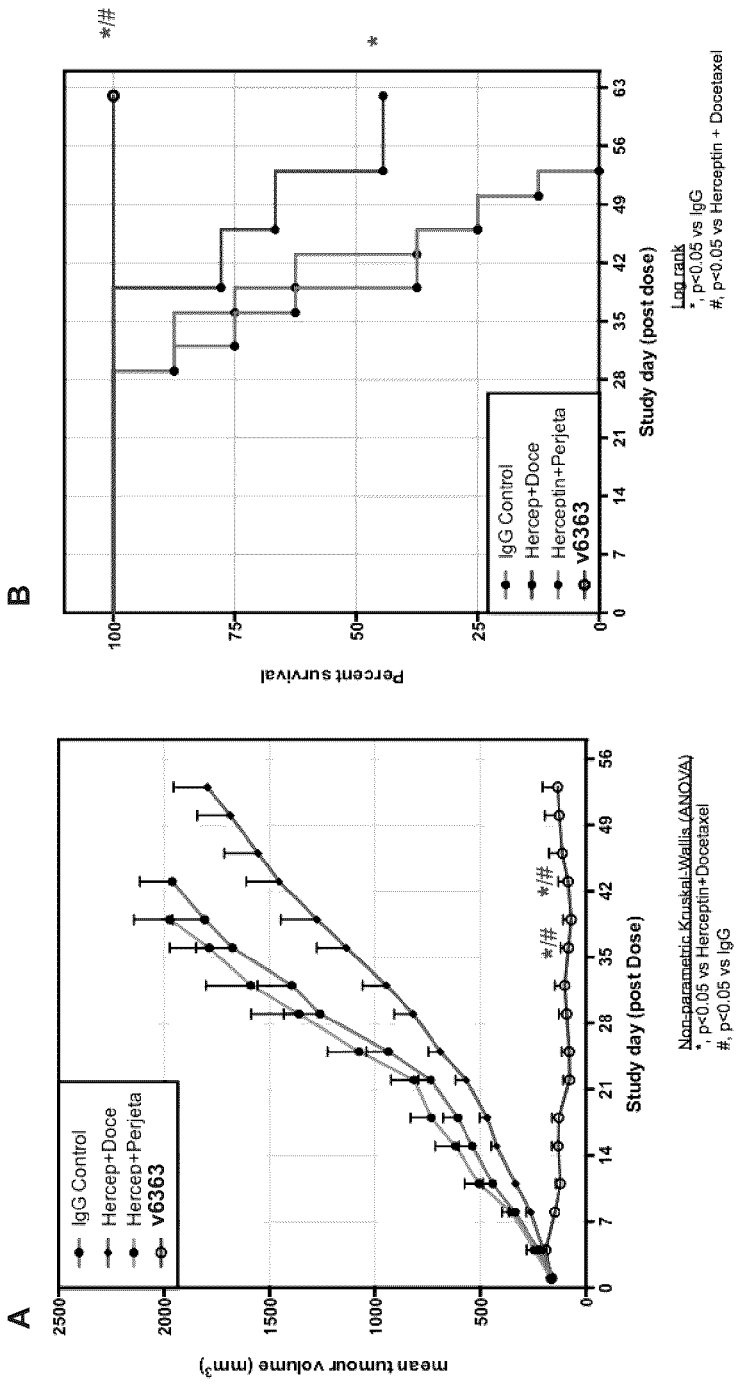

A
mean tumour volume (mm³)
2500
2000
1500
1000
500
0
0 7 14 21 28 35 42 49 56
Study day (post Dose)
IgG Control
Hercep+Doce
Hercep+Perjeta
v6363
*/#
*/#
*/#
Non-parametric Kruskal-Wallis (ANOVA)
*, p<0.05 vs Herceptin+Docetaxel
#, p<0.05 vs IgG
B
Percent survival
100
75
50
25
0
0 7 14 21 28 35 42 49 56 63
Study day (post dose)
IgG Control
Hercep+Doce
Herceptin+Perjeta
v6363
*/#
*
Log rank
*, p<0.05 vs IgG
#, p<0.05 vs Herceptin + Docetaxel

FIG. 33

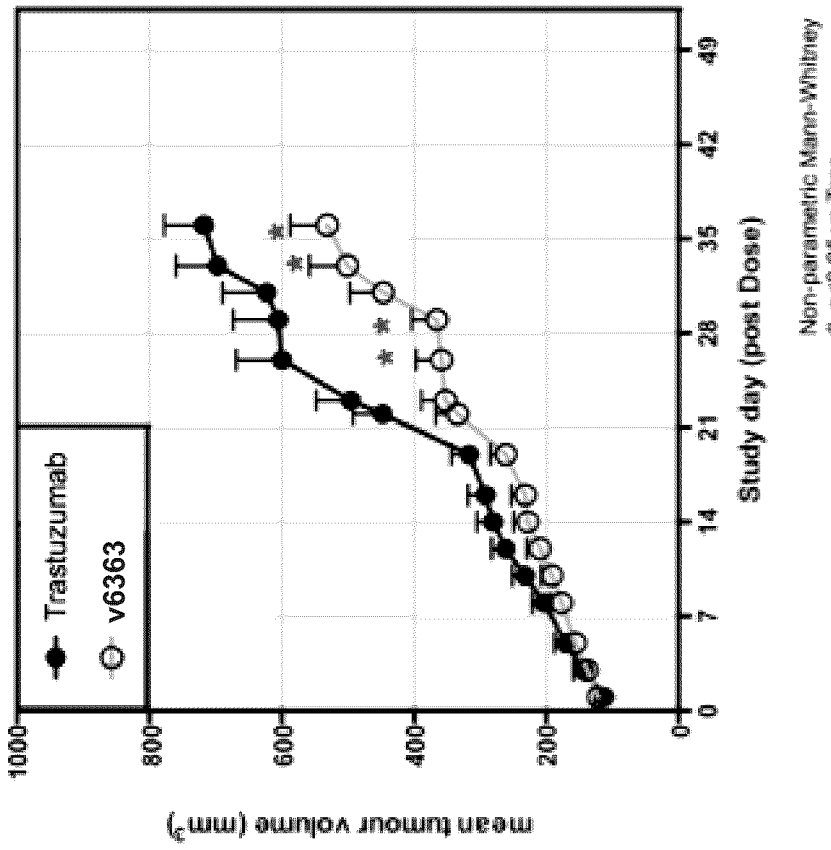

Trastuzumab
v6363
mean tumour volume (mm³)
1000
800
600
400
200
0
0
7
14
21
28
35
42
49
Study day (post Dose)
Non-parametric Mann-Whitney
#, p<0.05 vs Tras

FIG. 34

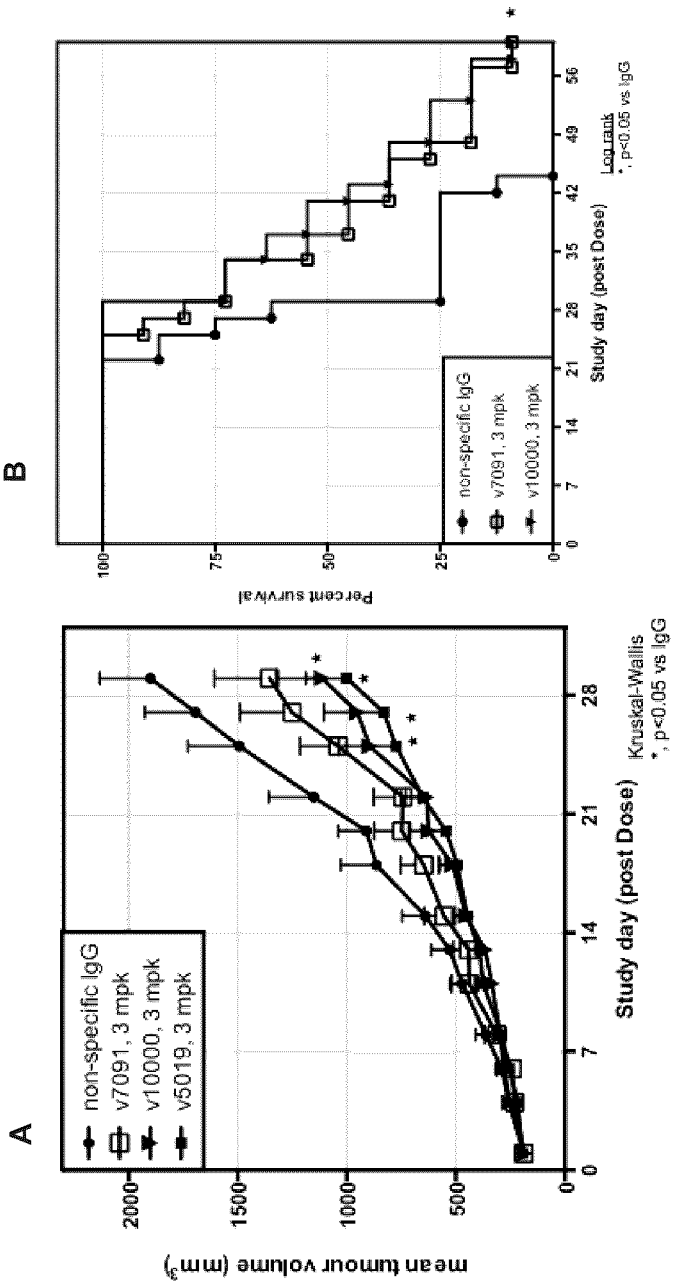

A
mean tumour volume (mm³)
2000
1500
1000
500
0
0
7
14
21
28
Study day (post Dose)
non-specific IgG
v7091, 3 mpk
v10000, 3 mpk
v5019, 3 mpk
Kruskal-Wallis
*, p<0.05 vs IgG
B
Percent survival
100
75
50
25
0
0
7
14
21
28
35
42
49
56
Study day (post Dose)
non-specific IgG
v7091, 3 mpk
v10000, 3 mpk
Log rank
*, p<0.05 vs IgG

FIG. 35

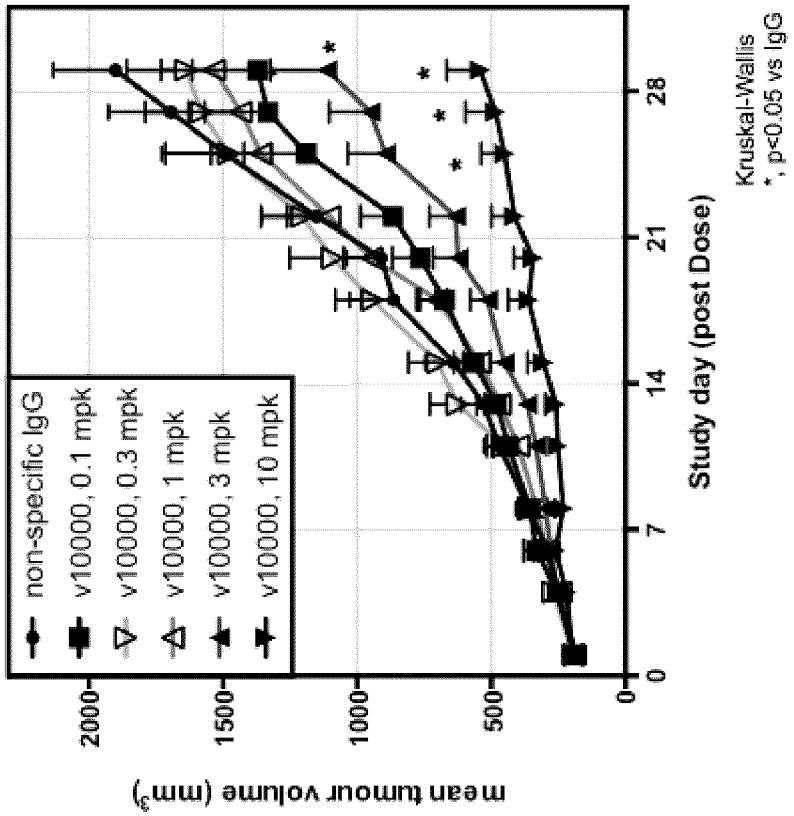

mean tumour volume (mm³)
2000
1500
1000
500
0
0
7
14
21
28
Study day (post Dose)
non-specific IgG
v10000, 0.1 mpk
v10000, 0.3 mpk
v10000, 1 mpk
v10000, 3 mpk
v10000, 10 mpk
Kruskal-Wallis
*, p<0.05 vs IgG

FIG. 36

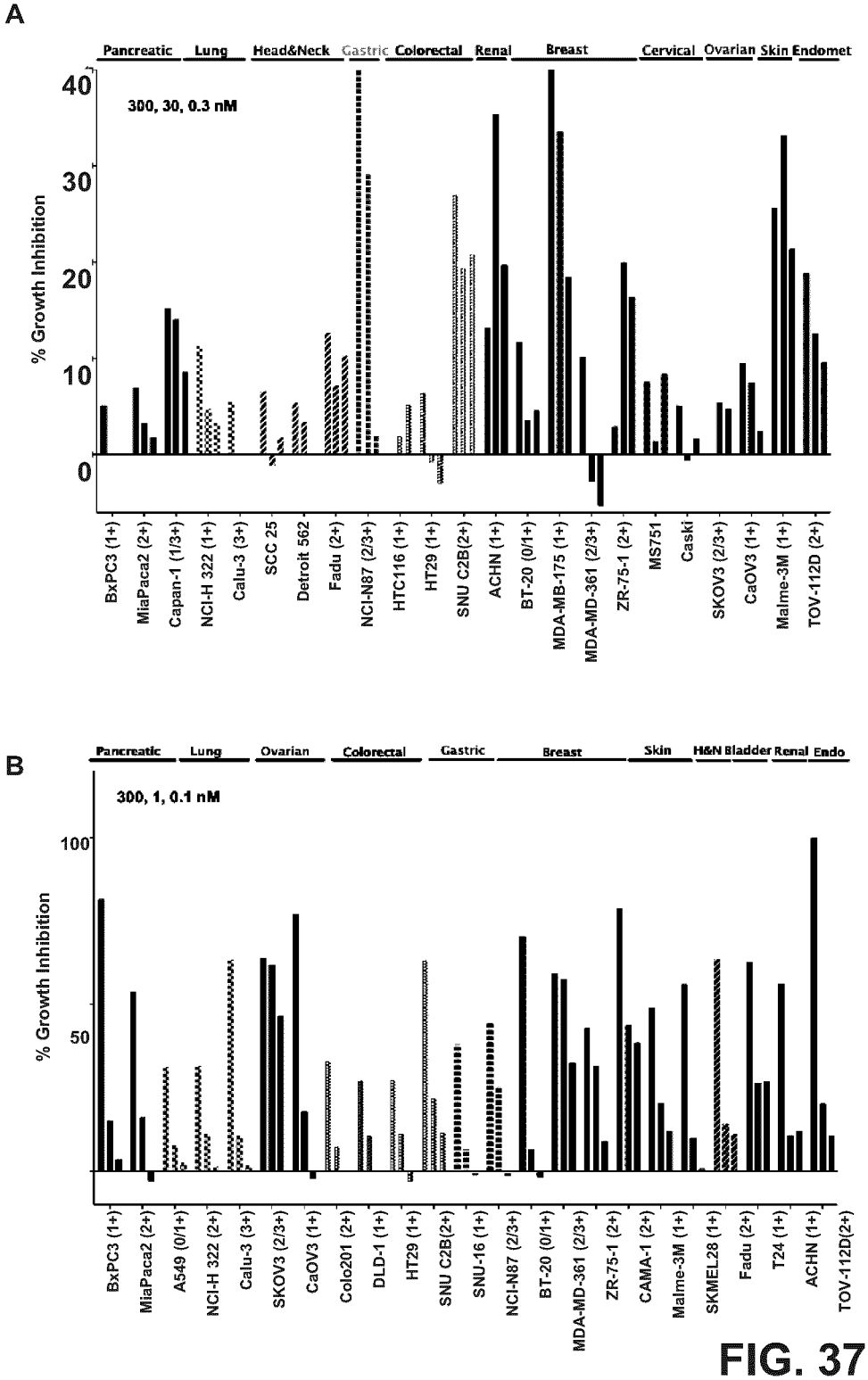
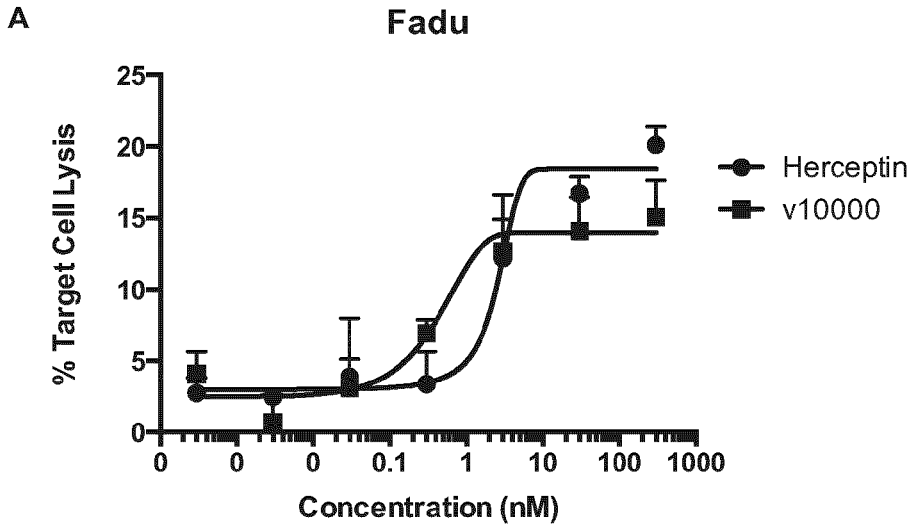

A
Pancreatic
Lung
Head&Neck
Gastric
Colorectal
Renal
Breast
Cervical
Ovarian
Skin
Endomet
300, 30, 0.3 nM
% Growth Inhibition
40
30
20
10
0
BxPC3 (1+)
MiaPaca2 (2+)
Capan-1 (1/3+)
NCI-H 322 (1+)
Calu-3 (3+)
SCC 25
Detroit 562
Fadu (2+)
NCI-N87 (2/3+)
HTC116 (1+)
HT29 (1+)
SNU C2B(2+)
ACHN (1+)
BT-20 (0/1+)
MDA-MB-175 (1+)
MDA-MD-361 (2/3+)
ZR-75-1 (2+)
MS751
Caski
SKOV3 (2/3+)
CaOV3 (1+)
Malme-3M (1+)
TOV-112D (2+)
B
Pancreatic
Lung
Ovarian
Colorectal
Gastric
Breast
Skin
H&N
Bladder
Renal
Endo
300, 1, 0.1 nM
% Growth Inhibition
100
50
BxPC3 (1+)
MiaPaca2 (2+)
A549 (0/1+)
NCI-H 322 (2+)
Calu-3 (3+)
SKOV3 (2/3+)
CaOV3 (1+)
Colo201 (2+)
DLD-1 (1+)
HT29 (1+)
SNU C2B(2+)
SNU-16 (1+)
NCI-N87 (2/3+)
BT-20 (0/1+)
MDA-MD-361 (2/3+)
ZR-75-1 (2+)
CAMA-1 (2+)
Malme-3M (1+)
SKMEL28 (1+)
Fadu (2+)
T24 (1+)
ACHN (1+)
TOV-112D(2+)

FIG. 37

Cell Line	Cell Line Description	IHC Receptor			V1000	V10553	Ref
		HER2	EGFR	HER3	activity	activity	
BxPC3	human pancreas adenocarcinoma	1	2	1	+	+	1,2,3
Capan-1	human pancreatic adenocarcinoma	1/3	1	0	+	+	1,4,5
MiaPaca2	human pancreas carcinoma	2	1/2	0	+	+	3,4
SW 1990	human pancreas adenocarcinoma, metastatic	2	1	0	-	+	2,4
Panc1	human pancreas carcinoma	1	1/2		-	+	4
A549	human lung carcinoma	0/1	1		-	+	6,7
Calu-3	human lung adenocarcinoma	3	2	1	+	+	6,8,9
Calu-6	human lung anaplastic carcinoma	0			-	+	6
NCI-H2126	human adenocarcinoma; non-small cell lung cancer				-	+	10
NCI-H322	human Caucasian bronchioalveolar carcinoma	2	2		+	+	6,7,11
Detroit 562	human pharyngeal carcinoma				+	+	12
SCC-15	human tongue squamous cell carcinoma		2		-	+	12
SCC-25	human tongue squamous cell carcinoma		2		+	+	12
FaDu	squamous cell carcinoma, pharynx	2	2		+	+	
Colo201	human colorectal adenocarcinoma	2	1		-	+	13
DLD-1	human colorectal adenocarcinoma, Dukes' type C	1	0/1		-	+	14
HCT116	human colorectal carcinoma	1	0/1		-	+	14
HT 29	human colorectal adenocarcinoma;	1	0		+	+	14
SNU-C2B	humancecum colorectal carcinoma	2*			+	+	
SNU-1	human gastric carcinoma	0			-	+	15
SNU-16	human gastric carcinoma	1			-	+	15
NCI-N87	human gastric carcinoma	3	2	1	+	+	15
MDAMB175	human breast ductal carcinoma, ER+	1	1	0/1	+	+	8,16
MDAMB361	human breast adenocarcinoma, ER+, HER2 amp	2/3	1	1	+	+	9,15,17
ZR-75-1	human breast duct epithelial ductal carcinoma, ER+ luminal A	2	1	1	-	+	9
BT-20	human breast carcinoma, Basal A TNBC	0/1	2	1	+	+	18
BT549	human breast ductal carcinoma, Basal B, Mesenchymal-like TNBC, ER-	0	0/1	0	-	+	18
CAMA-1	human breast adenocarcinoma, ER+	2	0	1	-	+	
MDAMB453	human breast metastatic carcinoma, ER-, HER2amp luminal A TNBC	0	0/1	0	-	+	18
T47D	human breast ductal carcinoma, ER+	1	0	1	-	+	19
SK-UT-1	human uterus mesodermal tumor (mixed) grade III				-	+	
TOV-112D	human primary malignant adenocarcinoma; endometrioid carcinoma	2	1	2	+	+	20
A431	human skin epidermoid carcinoma	1	3		-	+	21
Malme-3M	human malignant melanoma, metastatic lung	1	1	1	+	+	9, 22
SKMEL28	human malignant melanoma	1	0		-	+	22
Caski	human cervix carcinoma	1			+	+	23
MS751	human cervix epidermoid carcinoma				+	+	
T24	human urinary bladder carcinoma	1	0		-	+	19,21,24
ACHN	human renal cell adenocarcinoma	1	2	0/1	+	+	9, 25
CaOV3	human ovary adenocarcinoma	1	1		+	+	26
Ovcar-3	human ovary adenocarcinoma	1/2	2	2	-	+	20, 26
SKOV3	human ovary adenocarcinoma	2/3	2	0/1	-	+	

FIG. 38


A
Fadu
% Target Cell Lysis
25
20
15
10
5
0
0 0 0 0.1 1 10 100 1000
Concentration (nM)
Herceptin
v10000

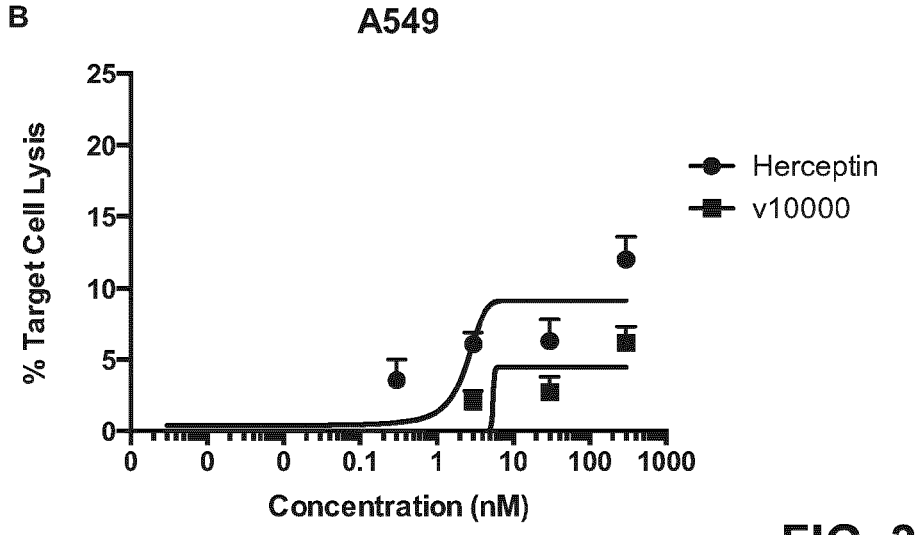
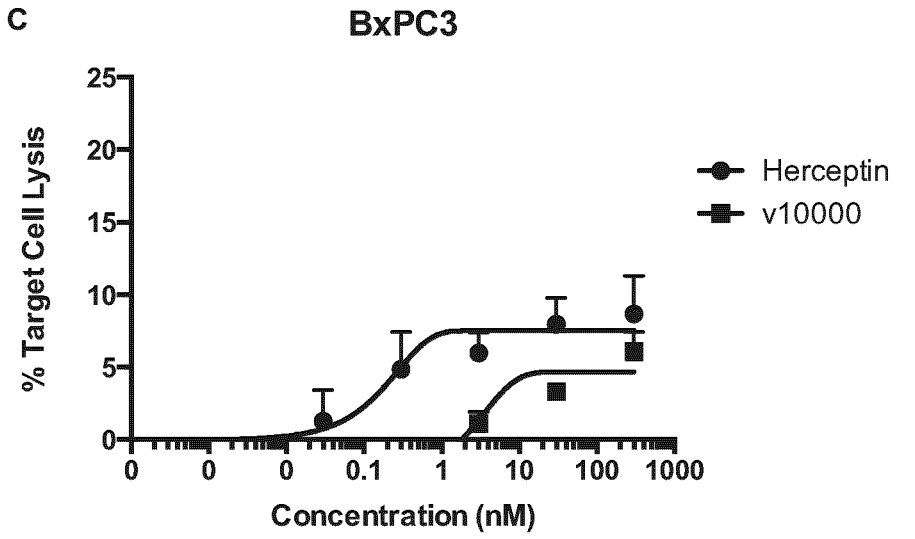

B
A549
% Target Cell Lysis
25
20
15
10
5
0
0 0 0 0.1 1 10 100 1000
Concentration (nM)
Herceptin
v10000

FIG. 39


C
BxPC3
% Target Cell Lysis
25
20
15
10
5
0
0 0 0 0.1 1 10 100 1000
Concentration (nM)
Herceptin
v10000

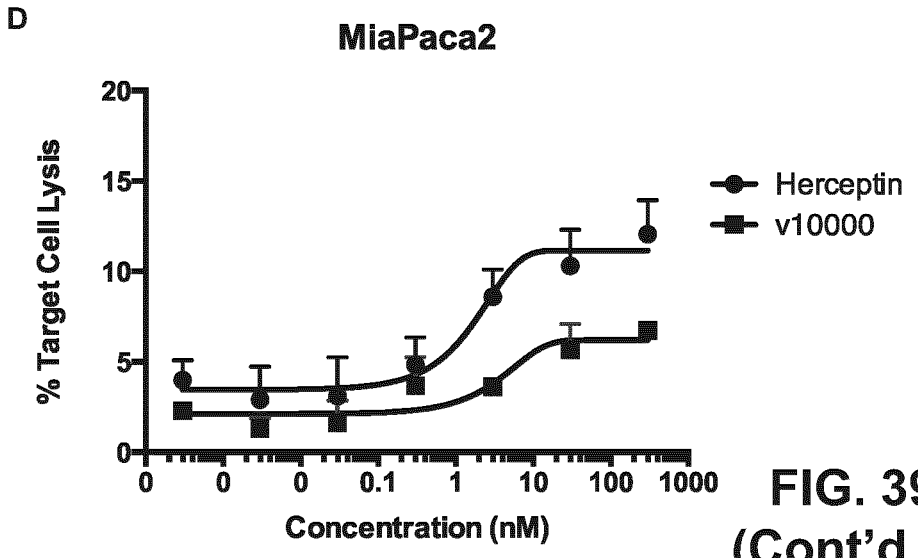

D
MiaPaca2
% Target Cell Lysis
20
15
10
5
0
0 0 0 0.1 1 10 100 1000
Concentration (nM)
Herceptin
v10000

FIG. 39
(Cont'd...)

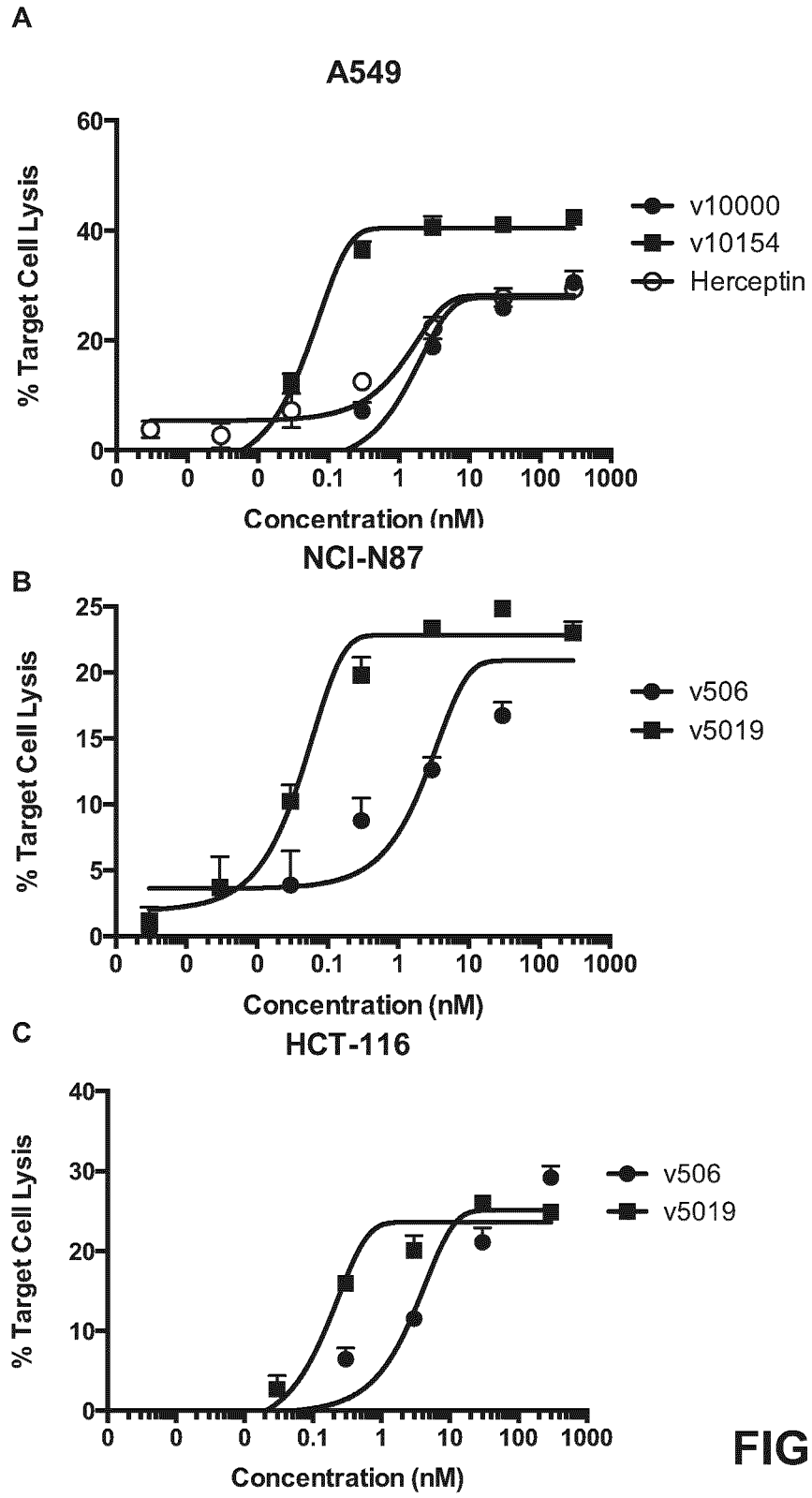

A
A549
% Target Cell Lysis
60
40
20
0
0 0 0 0.1 1 10 100 1000
Concentration (nM)
v10000
v10154
Herceptin
B
NCI-N87
% Target Cell Lysis
25
20
15
10
5
0
0 0 0 0.1 1 10 100 1000
Concentration (nM)
v506
v5019
C
HCT-116
% Target Cell Lysis
40
30
20
10
0
0 0 0 0.1 1 10 100 1000
Concentration (nM)
v506
v5019

FIG. 40

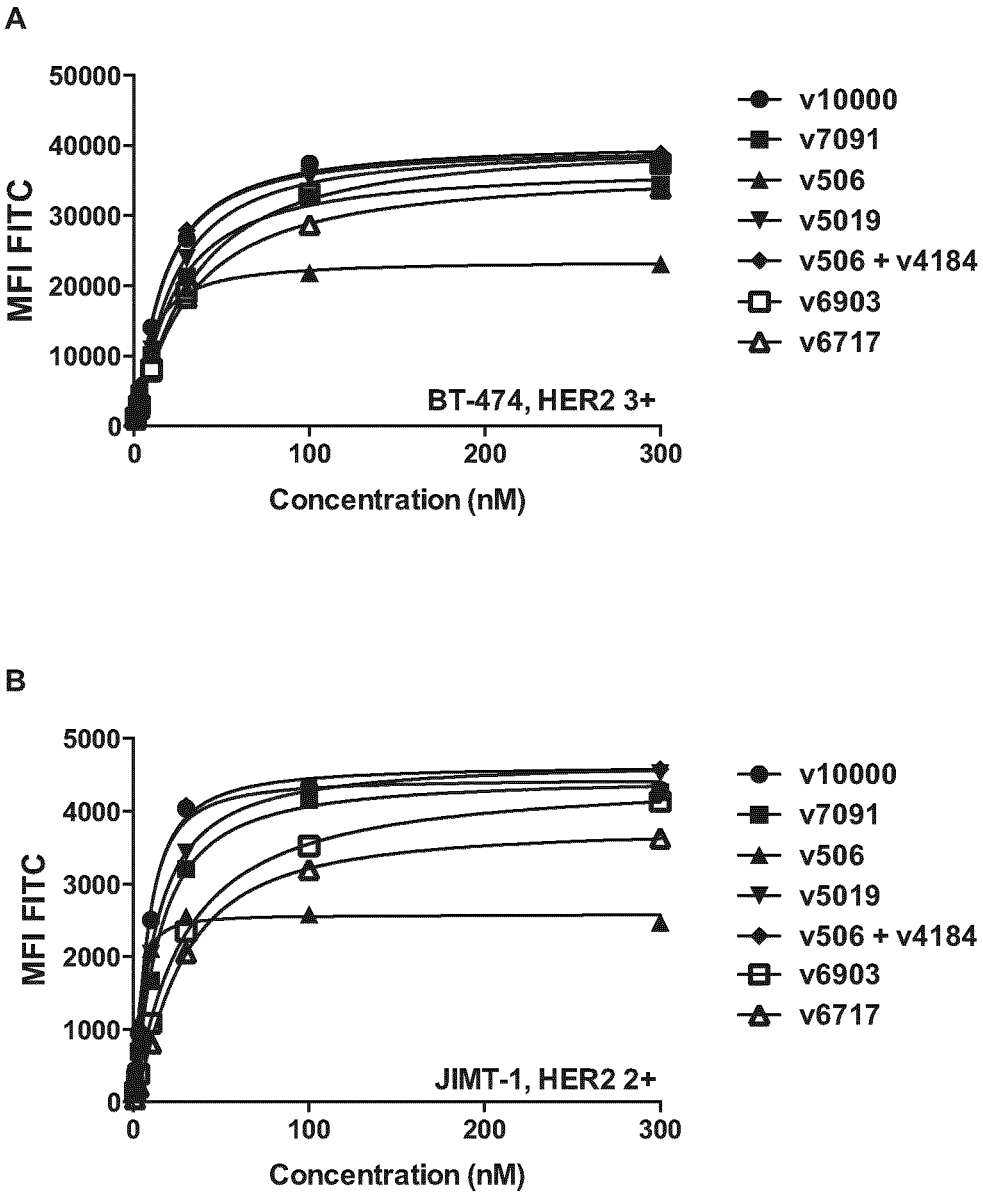
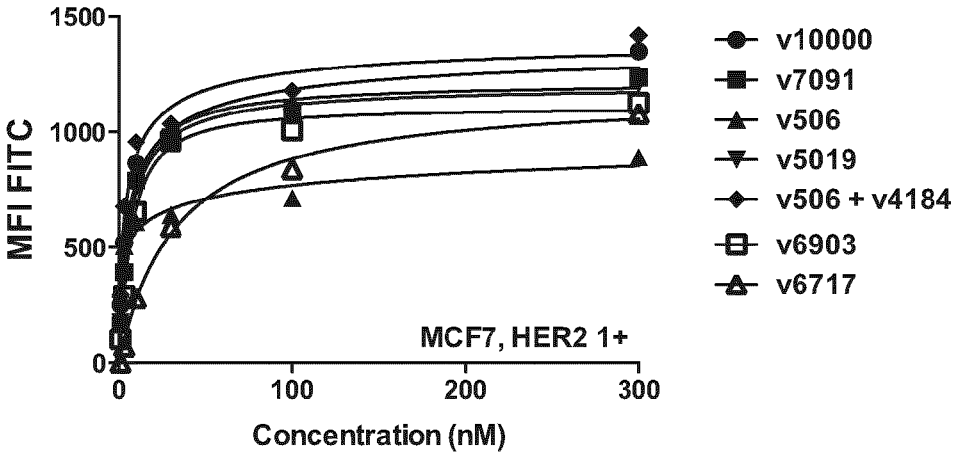

A
50000
40000
30000
20000
10000
0
MFI FITC
BT-474, HER2 3+
0
100
200
300
Concentration (nM)
v10000
v7091
v506
v5019
v506 + v4184
v6903
v6717
B
5000
4000
3000
2000
1000
0
MFI FITC
JIMT-1, HER2 2+
0
100
200
300
Concentration (nM)
v10000
v7091
v506
v5019
v506 + v4184
v6903
v6717

FIG. 41

C



D

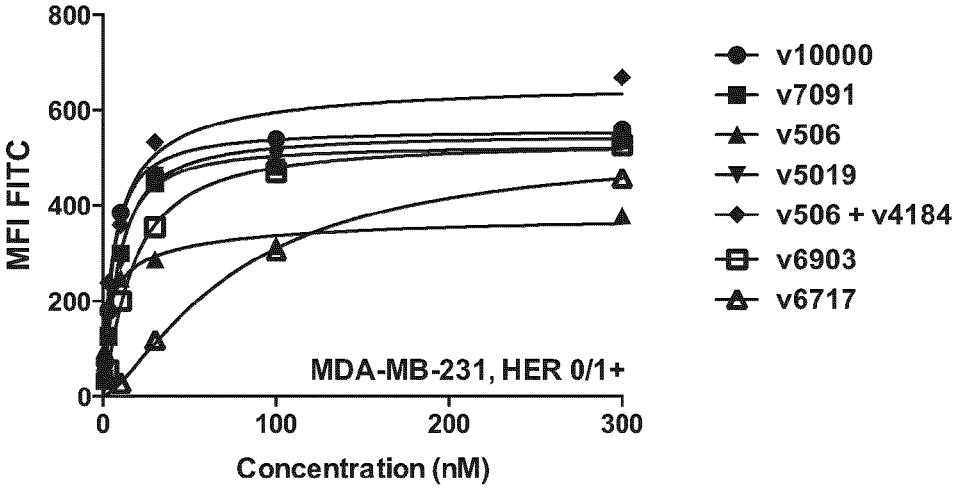


FIG. 41 (Cont'd...)

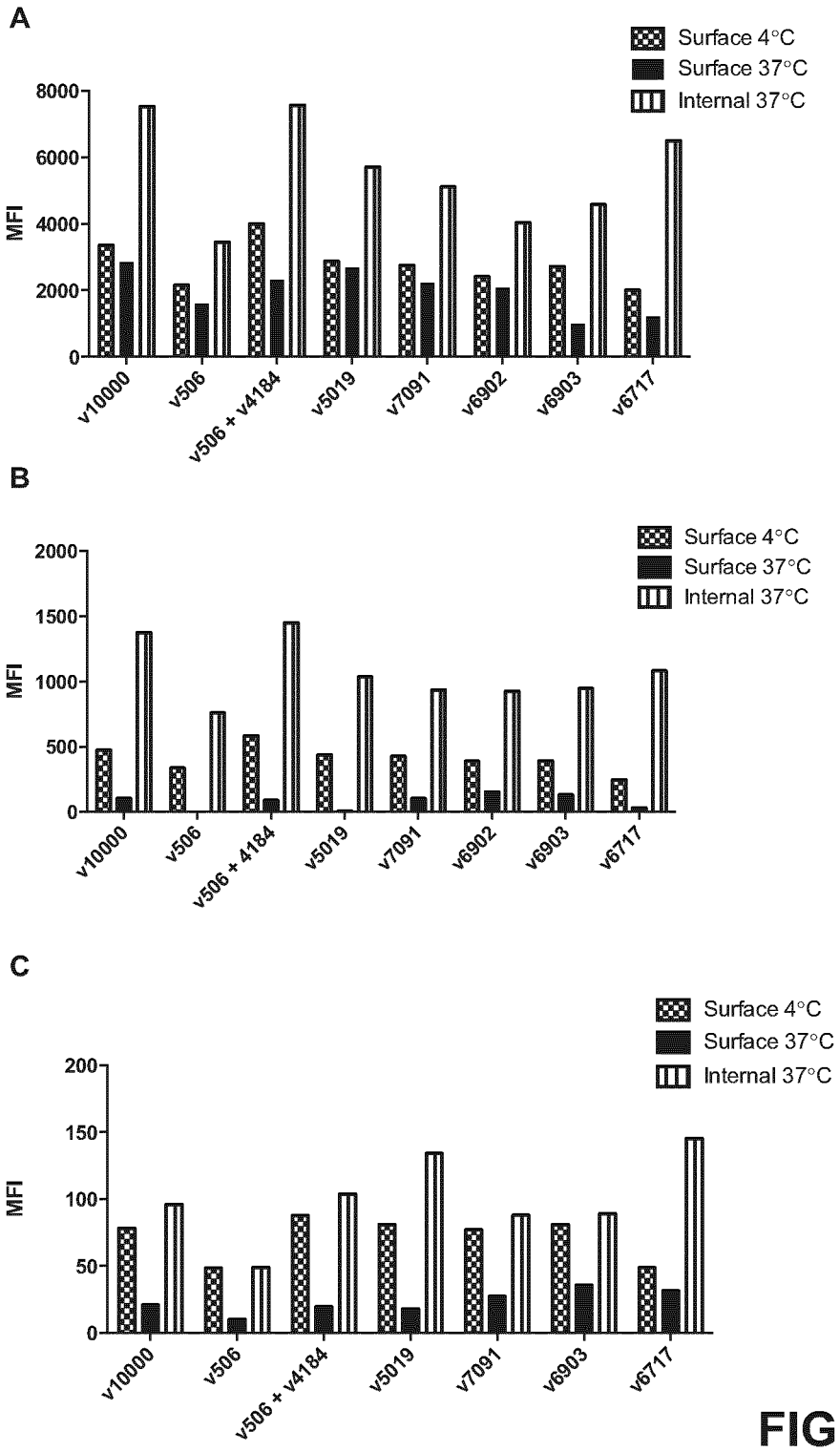
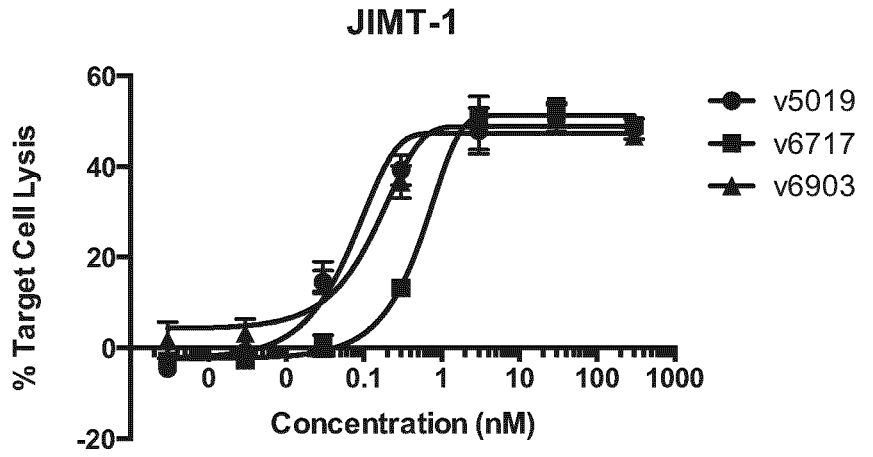

A
Surface 4°C
Surface 37°C
Internal 37°C
MFI
8000
6000
4000
2000
0
v10000
v506
v506 + v4184
v5019
v7091
v6902
v6903
v6717
B
Surface 4°C
Surface 37°C
Internal 37°C
MFI
2000
1500
1000
500
0
v10000
v506
v506 + 4184
v5019
v7091
v6902
v6903
v6717
C
Surface 4°C
Surface 37°C
Internal 37°C
MFI
200
150
100
50
0
v10000
v506
v506 + v4184
v5019
v7091
v6903
v6717

FIG. 42

A


JIMT-1
% Target Cell Lysis
60
40
20
0
-20
0
0
0.1
1
10
100
1000
Concentration (nM)
v5019
v6717
v6903

B

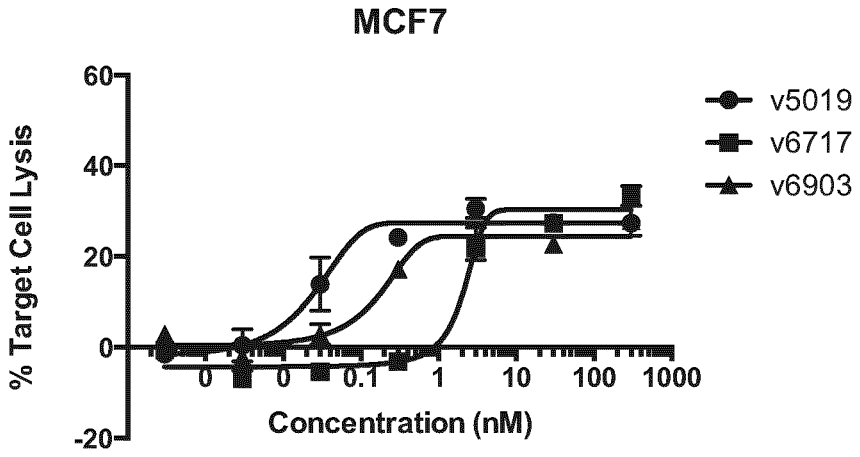

MCF7
% Target Cell Lysis
60
40
20
0
-20
0
0
0.1
1
10
100
1000
Concentration (nM)
v5019
v6717
v6903

FIG. 43

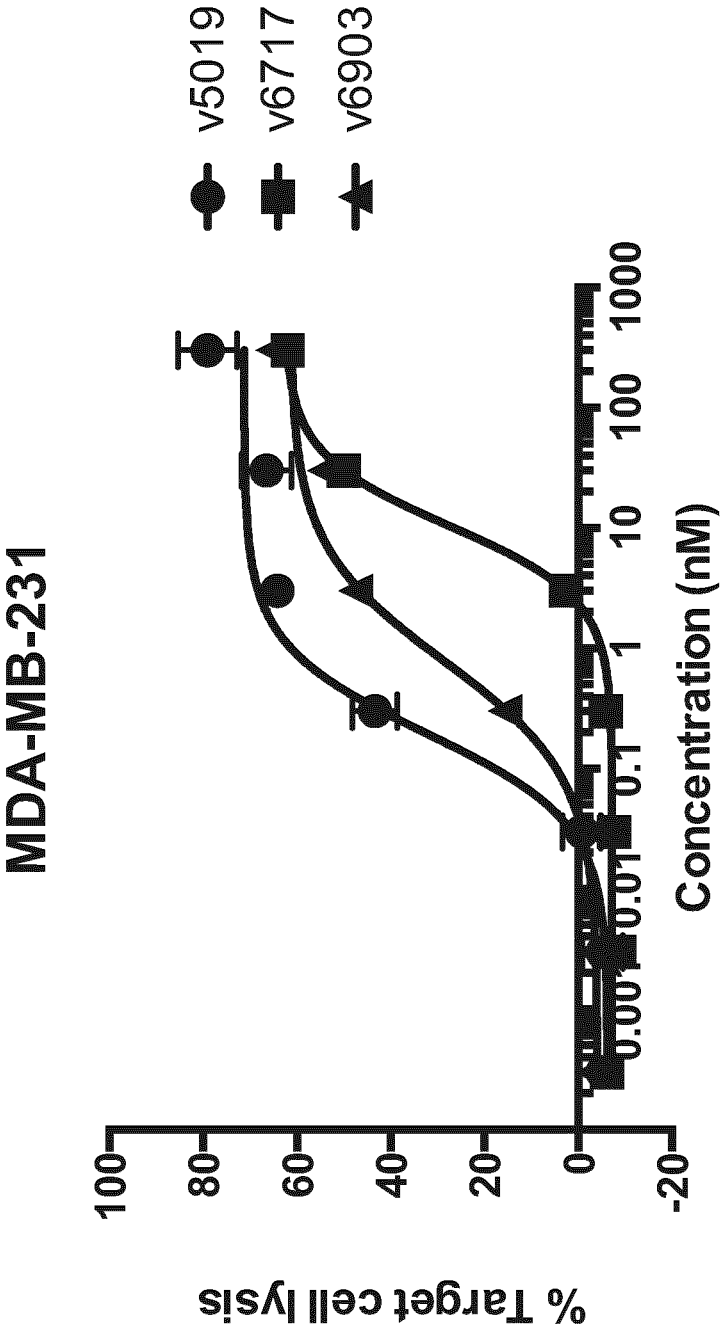

MDA-MB-231
v5019
v6717
v6903
% Target cell lysis
100
80
60
40
20
0
-20
0.001
0.01
0.1
1
10
100
1000
Concentration (nM)

FIG. 43C

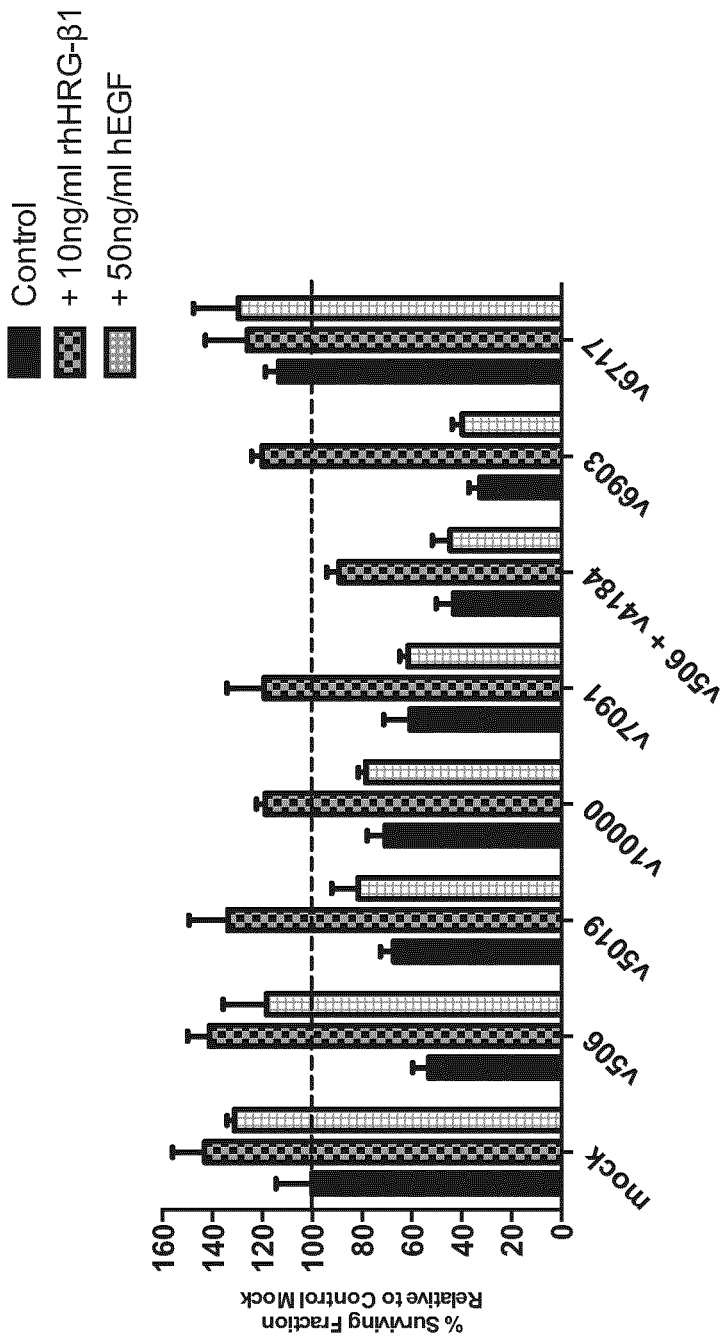

Control
+ 10ng/ml rhHRG-β1
+ 50ng/ml hEGF
% Surviving Fraction
Relative to Control Mock
0
20
40
60
80
100
120
140
160
mock
V506
V5019
V10000
V7091
V506 + V4184
V6903
V6717

FIG. 44

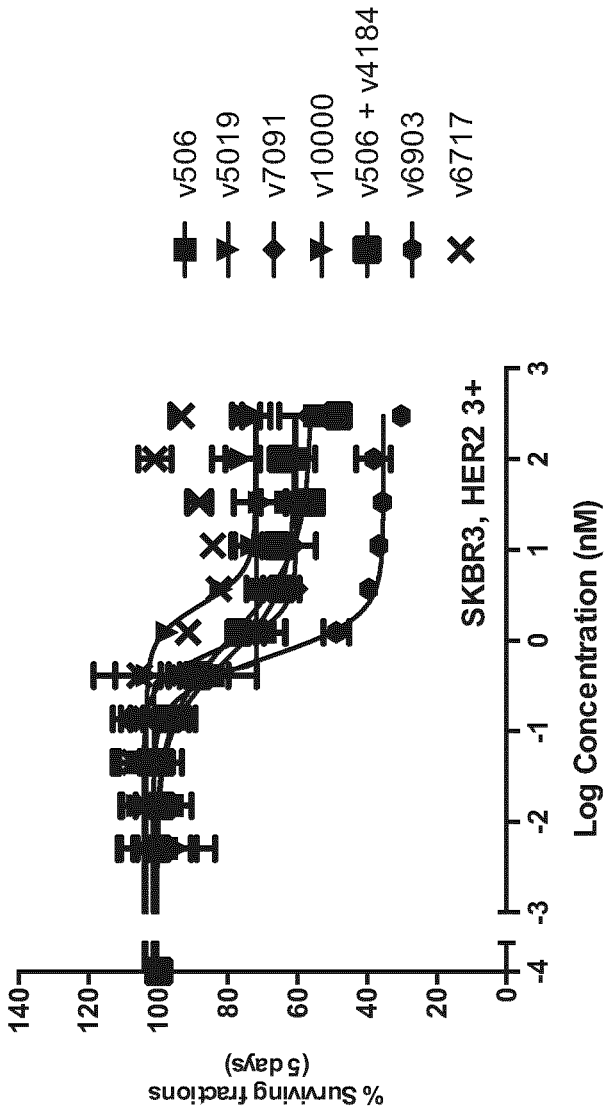

v506
v5019
v7091
v10000
v506 + v4184
v6903
v6717
SKBR3, HER2 3+
% Surviving fractions (5 days)
Log Concentration (nM)
140
120
100
80
60
40
20
0
-4
-3
-2
-1
0
1
2
3

FIG. 45

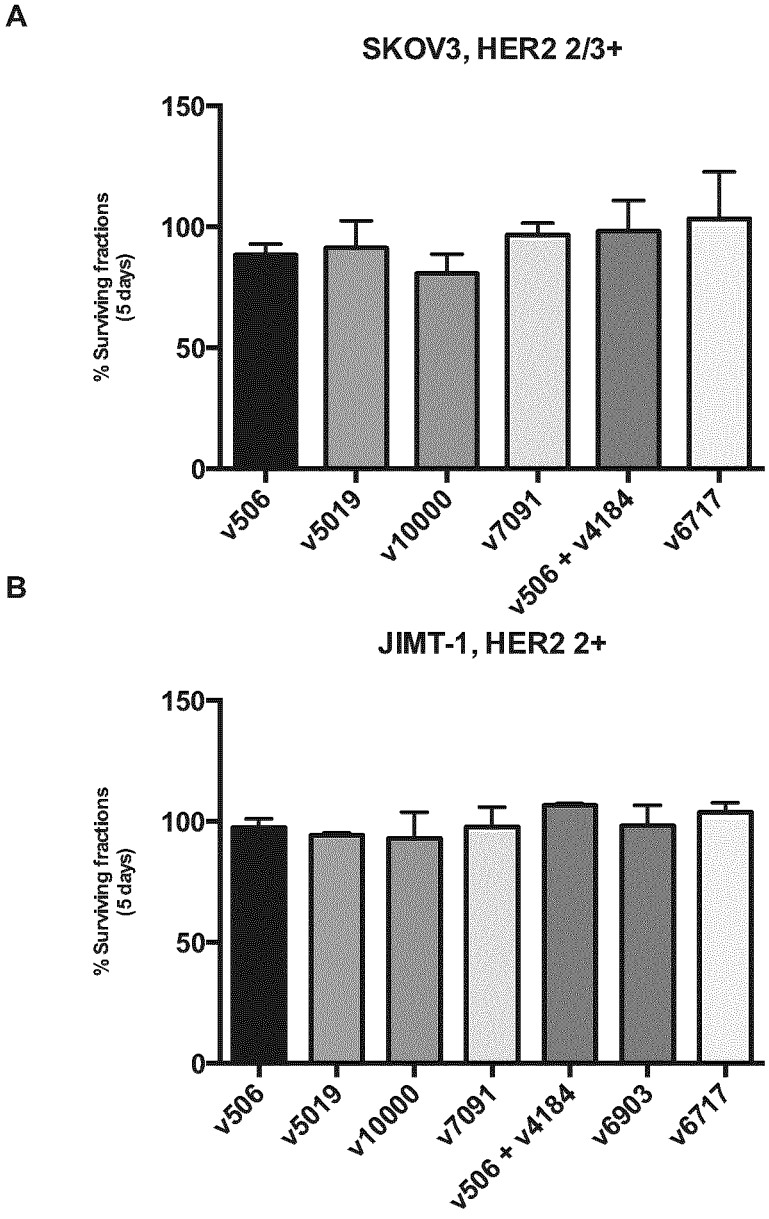

A
SKOV3, HER2 2/3+
% Surviving fractions (5 days)
150
100
50
0
v506
v5019
v10000
v7091
v506 + v4184
v6717
B
JIMT-1, HER2 2+
% Surviving fractions (5 days)
150
100
50
0
v506
v5019
v10000
v7091
v506 + v4184
v6903
v6717

FIG. 46

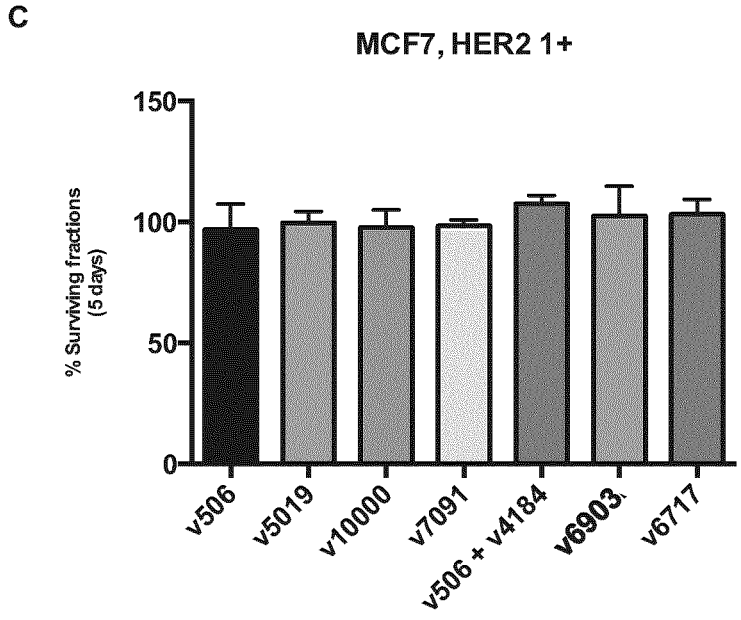
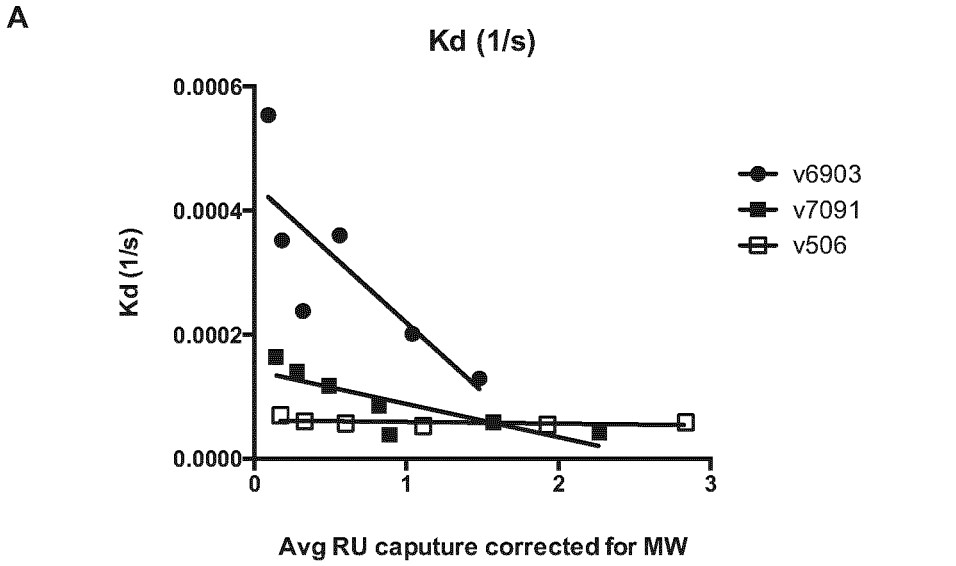

C
MCF7, HER2 1+
% Surviving fractions (5 days)
150
100
50
0
v506
v5019
v10000
v7091
v506 + v4184
v6903
v6717

FIG. 46 (Cont'd...)


A
Kd (1/s)
0.0006
0.0004
0.0002
0.0000
Kd (1/s)
0
1
2
3
Avg RU caputure corrected for MW
v6903
v7091
v506

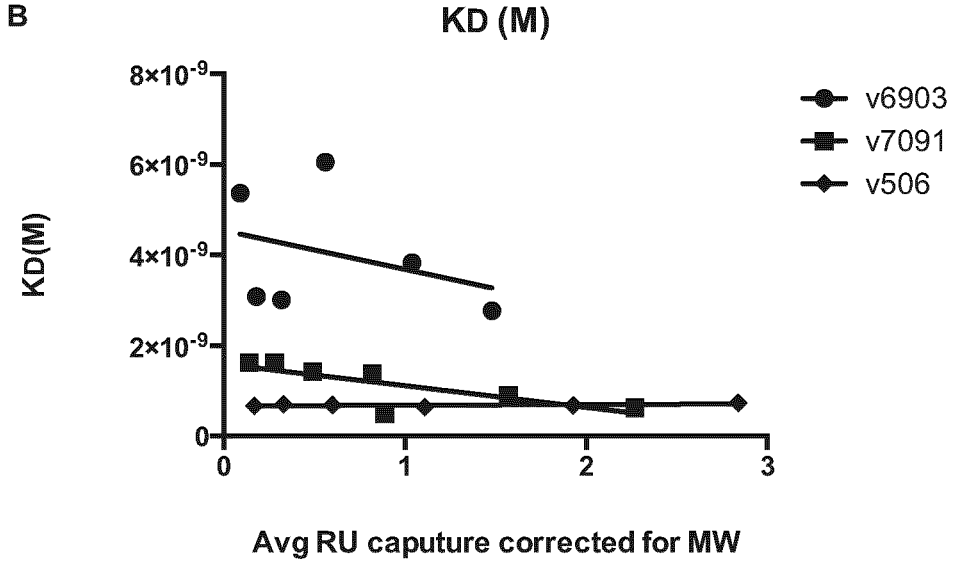

B
KD (M)
8×10-9
6×10-9
4×10-9
2×10-9
0
KD(M)
0
1
2
3
Avg RU caputure corrected for MW
v6903
v7091
v506

FIG. 47

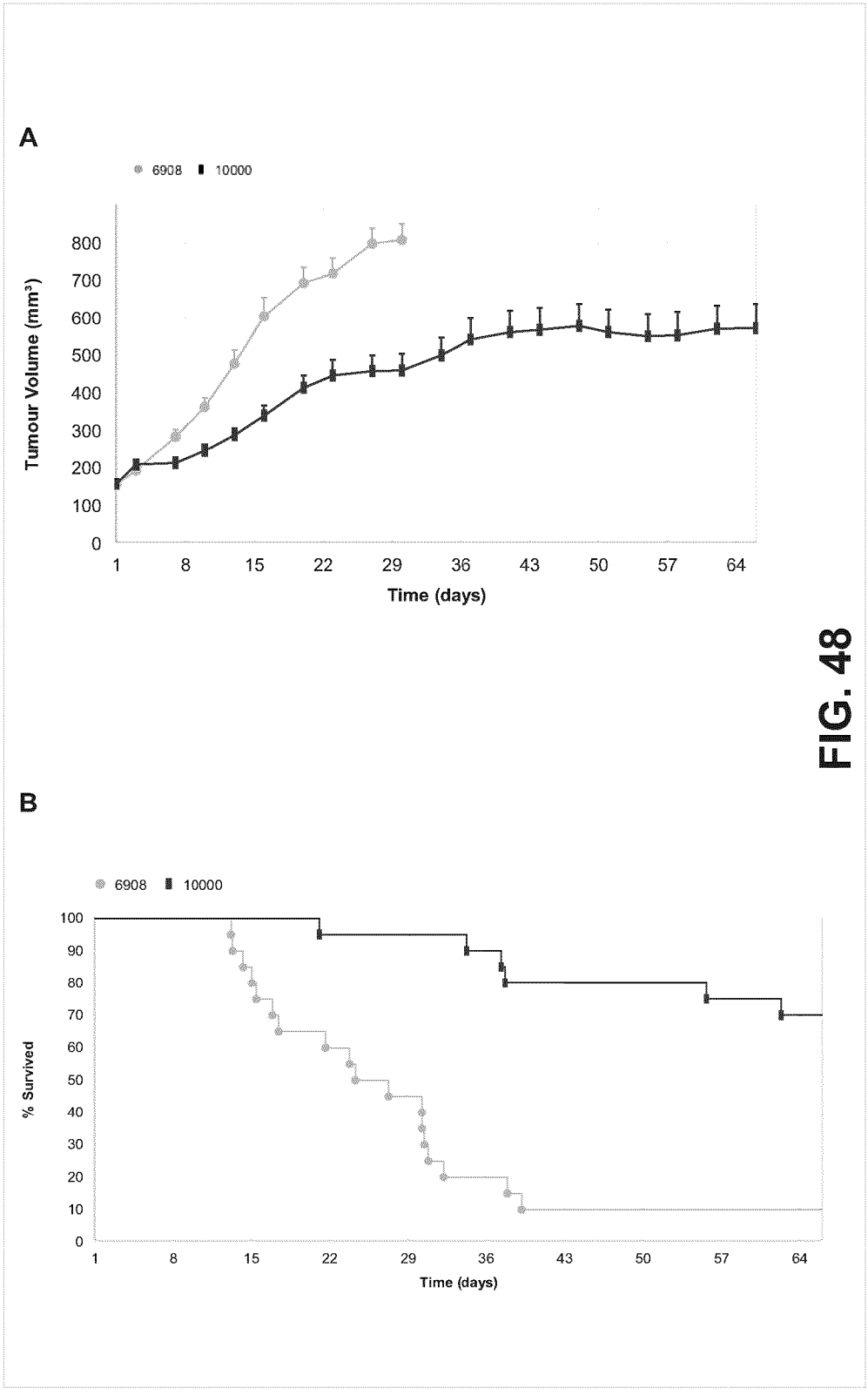

A
6908
10000
Tumour Volume (mm³)
800
700
600
500
400
300
200
100
0
1
8
15
22
29
36
43
50
57
64
Time (days)
B
6908
10000
% Survived
100
90
80
70
60
50
40
30
20
10
0
1
8
15
22
29
36
43
50
57
64
Time (days)

FIG. 48

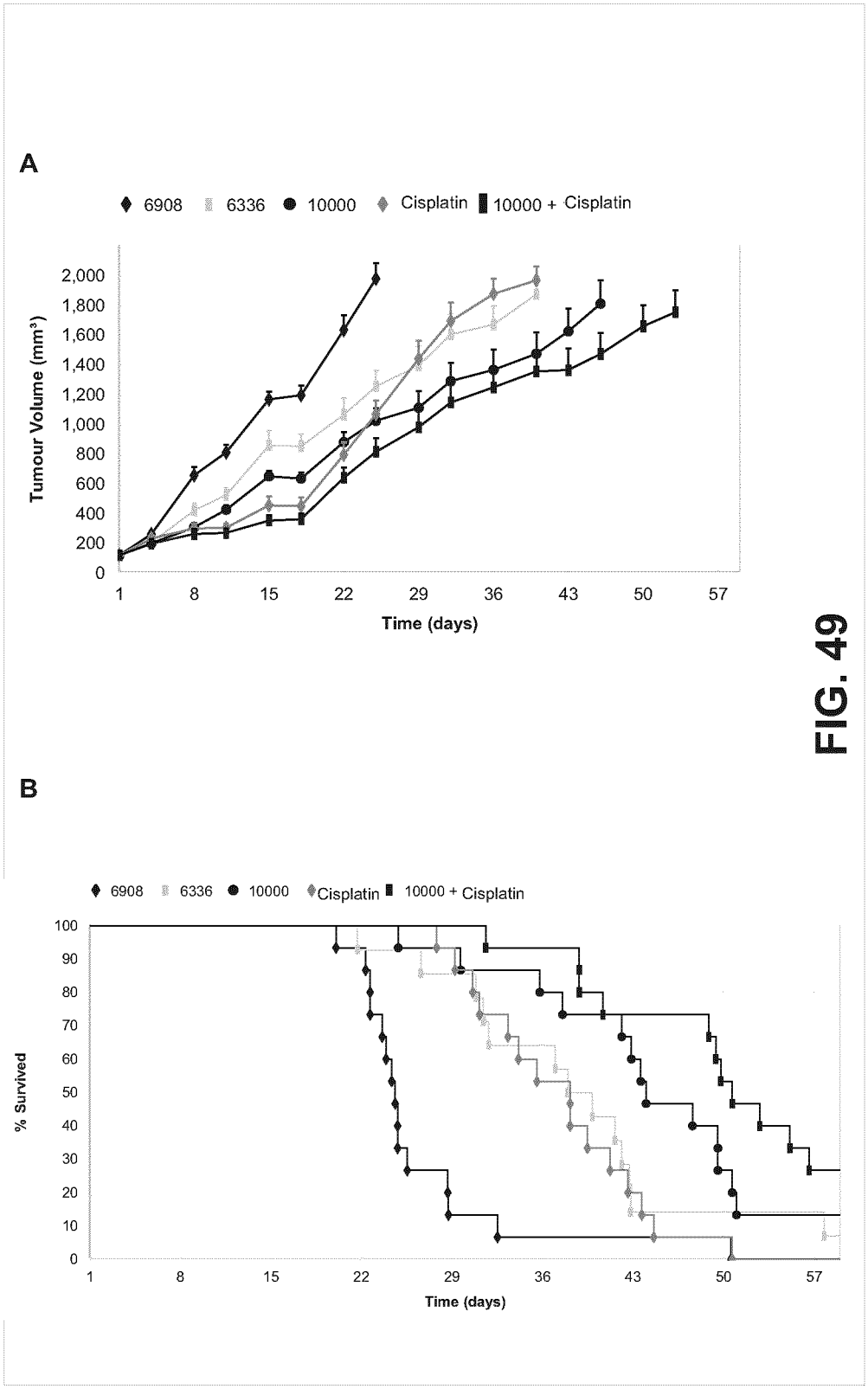

A
6908
6336
10000
Cisplatin
10000 + Cisplatin
Tumour Volume (mm³)
2,000
1,800
1,600
1,400
1,200
1,000
800
600
400
200
0
1
8
15
22
29
36
43
50
57
Time (days)
B
6908
6336
10000
Cisplatin
10000 + Cisplatin
% Survived
100
90
80
70
60
50
40
30
20
10
0
1
8
15
22
29
36
43
50
57
Time (days)

FIG. 49

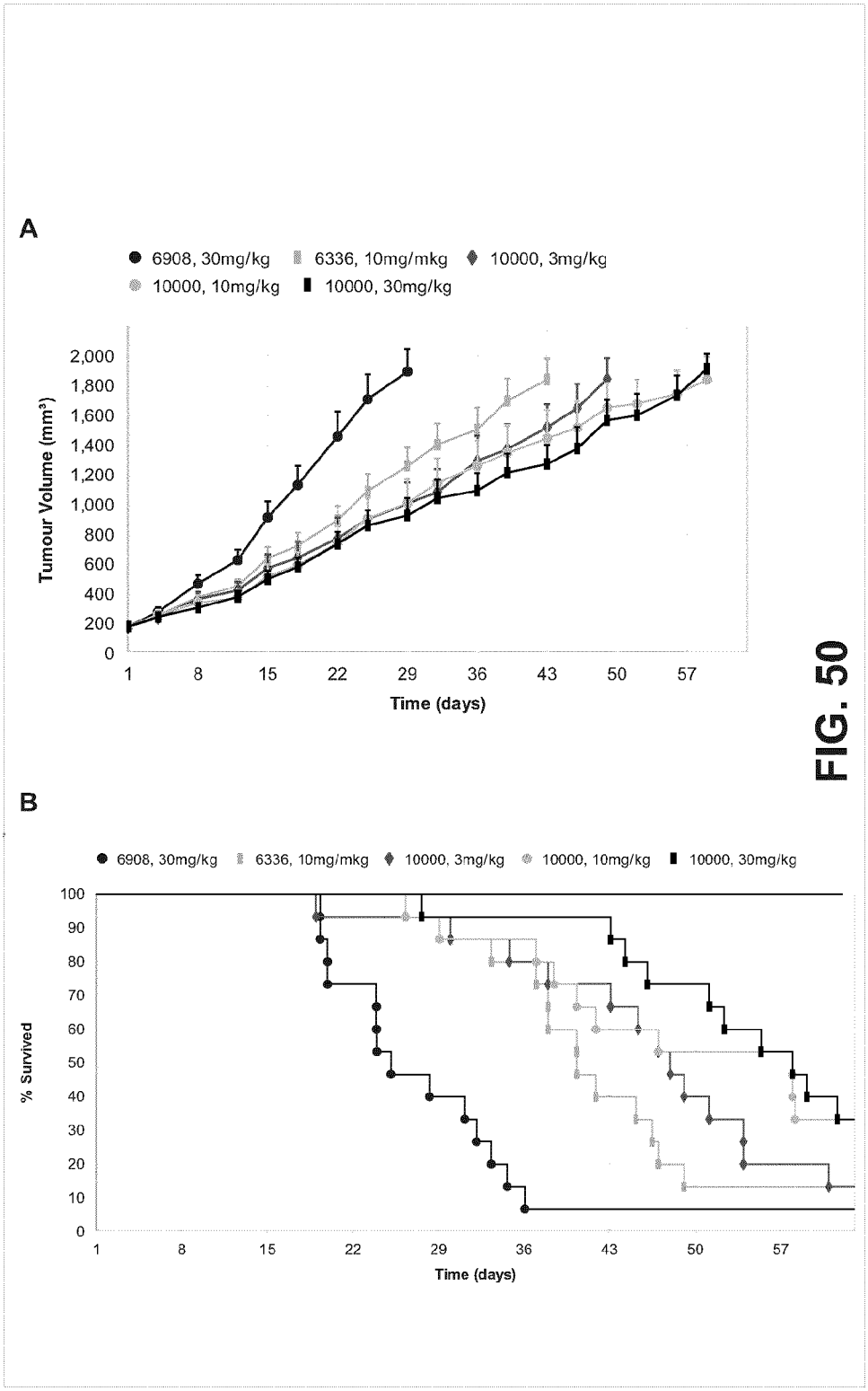

A
6908, 30mg/kg
6336, 10mg/mkg
10000, 3mg/kg
10000, 10mg/kg
10000, 30mg/kg
Tumour Volume (mm³)
2,000
1,800
1,600
1,400
1,200
1,000
800
600
400
200
0
1
8
15
22
29
36
43
50
57
Time (days)
B
6908, 30mg/kg
6336, 10mg/mkg
10000, 3mg/kg
10000, 10mg/kg
10000, 30mg/kg
% Survived
100
90
80
70
60
50
40
30
20
10
0
1
8
15
22
29
36
43
50
57
Time (days)

FIG. 50

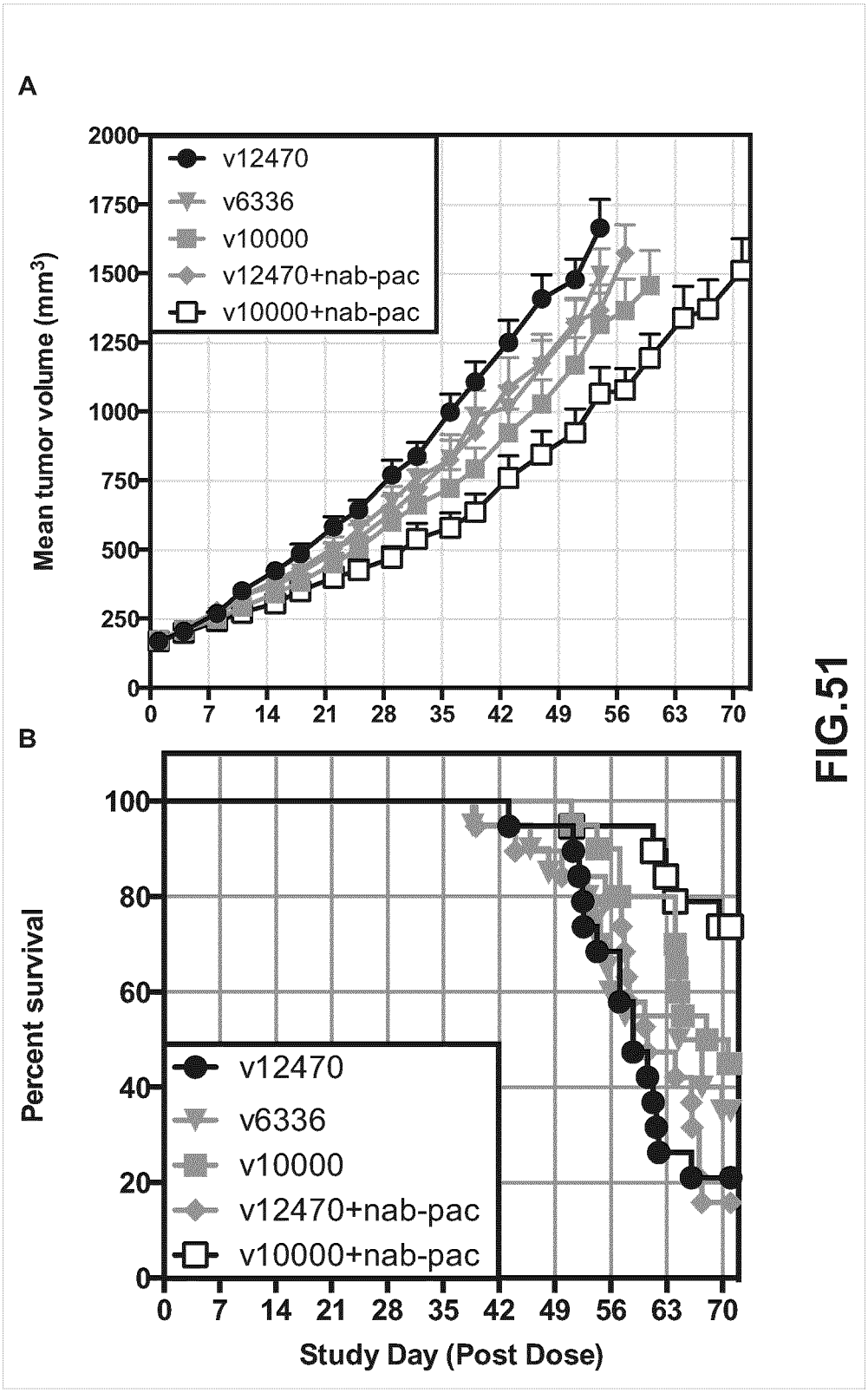

A
Mean tumor volume (mm3)
2000
1750
1500
1250
1000
750
500
250
0
v12470
v6336
v10000
v12470+nab-pac
v10000+nab-pac
0 7 14 21 28 35 42 49 56 63 70
B
Percent survival
100
80
60
40
20
0
v12470
v6336
v10000
v12470+nab-pac
v10000+nab-pac
0 7 14 21 28 35 42 49 56 63 70
Study Day (Post Dose)

FIG.51

A

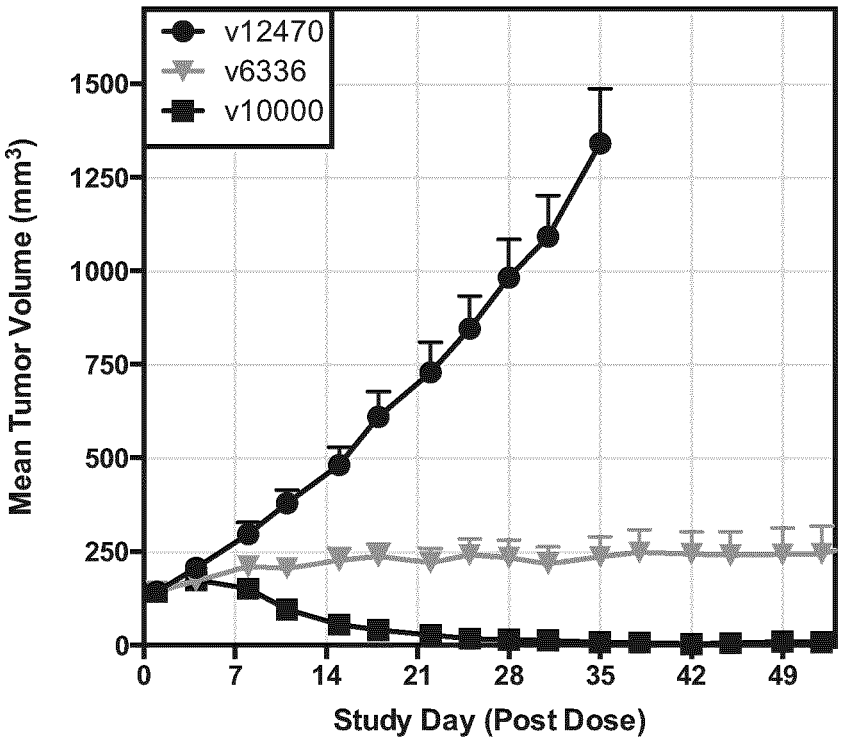

v12470
v6336
v10000
Mean Tumor Volume (mm3)
1500
1250
1000
750
500
250
0
0
7
14
21
28
35
42
49
Study Day (Post Dose)

FIG. 52

METHODS OF USING BISPECIFIC ANTIGEN-BINDING CONSTRUCTS TARGETING HER2

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of PCT/CA2014/051140, filed Nov. 27, 2014, and 62/166,844, filed May 27, 2015; each of which is herein incorporated by reference, in its entirety, for all purposes.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which will be submitted via EFS-Web and is hereby incorporated by reference in its entirety. Said ASCII copy, created on Nov. 24, 2015, is named 32565PCT_sequencelisting.txt, and is 275,091 bytes in size.

BACKGROUND

[0003] The majority of current marketed antibody therapeutics are bivalent monospecific antibodies optimized and selected for high affinity binding and avidity conferred by the two antigen-binding domains. Afucosylation or enhancement of FcgR binding by mutagenesis have been employed to render antibodies more efficacious via antibody Fc dependent cell cytotoxicity mechanisms. Afucyosylated antibodies or antibodies with enhanced FcgR binding still suffer from incomplete therapeutic efficacy in clinical testing and marketed drug status has yet to be achieved for any of these antibodies. Typical bivalent antibodies conjugated to toxins (antibody drug conjugates) are more efficacious but broader clinical utility is limited by dose-limiting toxicity.

[0004] Therapeutic antibodies would ideally possess certain minimal characteristics, including target specificity, biostability, bioavailability and biodistribution following administration to a subject patient, and sufficient target binding affinity and high target occupancy to maximize antibody dependent therapeutic effects. Typically therapeutic antibodies are monospecific. Monospecific targeting however does not address other target epitopes that may be relevant in signaling and disease pathogenesis, allowing for drug resistance and escape mechanism. Some of the current therapeutic paradigms call for the use of combination of two therapeutic monospecific antibodies targeting two different epitopes of the same target antigen. One example is the use of a combination of Trastuzumab and Pertuzumab, both targeting the HER2 receptor protein on the surface of some cancer cells, but patients still progress with disease while others with lower HER2 receptor levels (HER2 <3+ by Hercept test) show no therapeutic benefit. Therapeutic antibodies targeting HER2 are disclosed in WO 2012/143523 to GenMab and WO 2009/154651 to Genentech. Antibodies are also described in WO 2009/068625 and WO 2009/068631.

[0005] Co-owned patent application number PCT/CA2014/051140 describes HER2 antibodies. Co-owned patent application number PCT/US2014/037401 (WO 2014/182970) describes HER2 antibodies. Co-owned patent application number PCT/CA2013/050358 (WO 2013/166604) describes single arm monovalent antibodies. Co-owned patent applications PCT/CA2011/001238, filed Nov. 4, 2011, PCT/CA2012/050780, filed Nov. 2, 2012, PCT/CA2013/00471, filed May 10, 2013, and PCT/CA2013/050358, filed May 8, 2013 describe therapeutic antibodies. Each is hereby incorporated by reference in their entirety for all purposes.

SUMMARY

[0006] Described herein are methods of using one or more antigen-binding constructs to treat tumors in a subject, e.g., such as gastric, pancreatic, breast, lung, or head and neck tumors. The one or more antigen-binding constructs can comprise a first antigen-binding polypeptide construct which monovalently and specifically binds a HER2 (human epidermal growth factor receptor 2) ECD2 (extracellular domain 2) antigen on a HER2-expressing cell and a second antigen-binding polypeptide construct which monovalently and specifically binds a HER2 ECD4 (extracellular domain 4) antigen on a HER2-expressing cell, first and second linker polypeptides, wherein the first linker polypeptide is operably linked to the first antigen-binding polypeptide construct, and the second linker polypeptide is operably linked to the second antigen-binding polypeptide construct; wherein the linker polypeptides are capable of forming a covalent linkage with each other, wherein at least one of the ECD2- or the ECD4-binding polypeptide constructs is an scFv. In certain embodiments, the ECD2-binding polypeptide construct is an scFv, and the ECD2-binding polypeptide construct is a Fab. In certain embodiments, the ECD2-binding polypeptide construct is a Fab and the ECD4 binding polypeptide construct is an scFv. In some embodiments, both the ECD2- and ECD4-binding polypeptide constructs are scFvs. In some embodiments, the antigen-binding constructs have a dimeric Fc comprising a CH3 sequence. In some embodiments, the Fc is a heterodimer having one or more modifications in the CH3 sequence that promote the formation of a heterodimer with stability comparable to a wild-type homodimeric Fc. In some embodiments, the heterodimeric CH3 sequence has a melting temperature (Tm) of 68° C. or higher.

BRIEF DESCRIPTION OF THE DRAWINGS

[0007] FIG. **1**A depicts the structure of a biparatopic antibody in a Fab-Fab format. FIGS. **1**B to **1**E depict the structure of possible versions of a biparatopic antibody in an scFv-Fab format. In FIG. **1**B, antigen-binding domain 1 is an scFv, fused to Chain A, while antigen-binding domain 2 is a Fab, fused to Chain B. In FIG. **1**C, antigen-binding domain 1 is a Fab, fused to Chain A, while antigen-binding domain 2 is an scFv, fused to Chain B. In FIG. **1**D, antigen-binding domain 2 is a Fab, fused to Chain A, while antigen-binding domain 1 is an scFv, fused to Chain B. In FIG. **1**E, antigen-binding domain 2 is an scFv, fused to Chain A, while antigen-binding domain 1 is a Fab, fused to Chain B. In FIG. **1**F, both antigen-binding domains are scFvs.

[0008] FIG. **2** depicts the characterization of expression and purification of exemplary anti-HER2 biparatopic antibodies. FIG. **2**A and FIG. **2**B depict the SEC chromatograph of the protein A purified antibody, and non-reducing SDS-PAGE analysis of 10 L expression and purification of v5019. FIG. **2**C depicts the SDS-PAGE analysis of a 25 L expression and purification of v10000.

[0009] FIG. **3** depicts the results of UPLC-SEC analysis of exemplary anti-HER2 biparatopic antibodies purified by protein A and SEC. FIG. **3**A shows the results for v5019, where the upper panel shows the results of the purification

and the lower panel shows the same result with an expanded scale for the y-axis. A summary of the data obtained is provided below the UPLC-SEC results. FIG. **3**B shows the results for v10000.

[0010] FIG. **4** depicts LCMS analysis of the heterodimer purity of exemplary anti-HER2 biparatopic antibodies. FIG. **4**A depicts results from LC-MS analysis of the pooled SEC fractions of v5019. FIG. **4**B depicts the results from LC-MS analysis of the pooled protein A fractions of v10000.

[0011] FIG. **5** depicts analysis of a 25 L-scale preparation of an exemplary anti-HER2 biparatopic antibody. FIG. **5**A depicts the SDS-PAGE profile of an exemplary anti-HER2 biparatopic following MabSelect™ and HiTrap™ SP FF purification. FIG. **5**B depicts LCMS analysis of the purified antibody.

[0012] FIG. **6** compares the ability of an exemplary biparatopic anti-HER2 antibodies to bind to HER2+ whole cells displaying different HER2 receptor density compared to control antibodies, as measured by FACS. FIG. **6**A and FIG. **6**E depict binding to SKOV3 cells;

[0013] FIG. **6**B depicts binding to JIMT1 cells; FIG. **6**C and FIG. **6**F depict binding to MCF7 cells; FIG. **6**D depicts binding to MDA-MB-231 cells; and FIG. **6**G depicts binding to WI-38 cells.

[0014] FIG. **7** depicts the ability of exemplary anti-HER2 biparatopic antibodies to inhibit the growth of HER2+ cells. FIG. **7**A and FIG. **7**D shows growth inhibition in SKOV3 cells; FIG. **7**B shows growth inhibition in BT-474 cells; FIG. **7**C shows growth inhibition in SKBR3 cells, and FIG. **7**E shows growth inhibition in JIMT-1 cells.

[0015] FIG. **8** depicts the SPR binding data relating to the paratopes of an exemplary anti-HER2 biparatopic antibodies. FIG. **8**A illustrates the K_D values (nM) of a monovalent anti-Her2 antibody (v1040; representing the antigen-binding domain on CH—B of exemplary anti-Her2 biparatopic antibody), for binding to immobilized Her2 ECD or dimeric Her2-Fc. FIG. **8**B illustrates the K_D values (nM) of a monovalent anti-Her2 antibody (v4182; representing the antigen-binding domain on CH-A of exemplary anti-Her2 biparatopic antibody) for binding to immobilized Her2 ECD or dimeric Her2-Fc.

[0016] FIG. **9** depicts the ability of exemplary anti-HER2 biparatopic antibody to internalize in HER2+ cells. FIG. **9**A depicts internalization in BT-474 cells, while FIG. **9***b* depicts internalization in JIMT-1 cells.

[0017] FIG. **10** depicts surface binding and internalization of exemplary anti-HER2 biparatopic antibodies. FIG. **10**A (v5019) depicts the result in BT-474 cells; FIG. **10**B (v5019) and FIG. **10**F (v5019 and v10000) depict the result in JIMT1 cells; FIG. **10**C (v5019) and FIG. **10**E (v5019 and v10000) depict the result in SKOV3 cells, and FIG. **10**D (v5019) depicts the result in MCF7 cells.

[0018] FIG. **11** depicts the ability of an exemplary anti-HER2 biparatopic antibody to mediate ADCC in SKOV3 cells. In FIG. **11**A, the assay was carried out using an effector to target cell ratio of 5:1; in FIG. **11**B, the assay was carried out using an effector to target cell ratio of 3:1; and in FIG. **11**C, the assay was carried out using an effector to target cell ratio of 1.1.

[0019] FIG. **12** depicts the characterization of affinity and binding kinetics of monovalent anti-HER2 (v630 and v4182) and an exemplary biparatopic anti-Her2 antibody (v5019) to recombinant human HER2. FIG. **12**A shows the measurement of ka (1/Ms). FIG. **12**B shows the measurement of kd (1/s). FIG. **12**C shows the measurement of K_D (M).

[0020] FIG. **13** depicts affinity and binding characteristics of an exemplary biparatopic anti-HER2 antibody to recombinant human HER2 over a range of antibody capture levels. FIG. **13**A depicts the measurement of kd (1/s) to HER2 ECD determined over a range of antibody capture levels for exemplary biparatopic anti-Her2 antibody (v5019). FIG. **13**B depicts the measurement of kd (1/s) to HER2 ECD determined over a range of antibody capture levels for monovalent anti-Her2 antibody (v4182). FIG. **13**C depicts the measurement of kd (1/s) to HER2 ECD determined over a range of antibody capture levels for monovalent anti-Her2 antibody (v630).

[0021] FIG. **14** shows a comparison of the mechanism of binding of a monospecific anti-ECD4 HER2 antibody (left), and a Fab-scFv biparatopic anti-ECD2×ECD4 HER2 antibody (right). The monospecific anti-ECD4 HER2 antibody is capable of binding one antibody molecule to two HER2 molecules; whereas the biparatopic anti-ECD2×ECD4 HER2 antibody is capable of binding one antibody to two HER2 molecule, as well as 2 antibodies to one HER2 molecule and combinations therein which results in HER2 receptor cross-linking and lattice formation followed by downstream biological effects such as internalization and/or growth inhibition as indicated by the arrows. IEC represents "immune effector cells." The four extracellular domains of HER2 are numbered as 1, 2, 3, or 4 where 1=ECD1, 2=ECD2, 3=ECD3, and 4=ECD4.

[0022] FIG. **15** depicts the effect of an exemplary anti-HER2 biparatopic antibody on AKT phosphorylation in BT-474 cells.

[0023] FIG. **16** depicts the effect of an exemplary anti-HER2 biparatopic antibody on cardiomyocyte viability. FIG. **16**A depicts the effect of v5019 and the corresponding ADC v6363 on cardiomyocyte viability; FIG. **16**B depicts the effect of v5019, v7091, and v10000 and corresponding ADCs v6363, 7148, 10553 on cardiomyocyte viability, and FIG. **16**C depicts the effect of v5019, v7091, and v10000 and corresponding ADCs v6363, 7148, 10553 on the viability of doxorubicin-pretreated cardiomyocytes.

[0024] FIG. **17** depicts the ability of exemplary anti-HER2 biparatopic antibody drug conjugates to inhibit the growth of HER2+ cells. FIG. **17**A shows the ability of the ADC v6363 to inhibit the growth of JIMT1 cells. FIG. **17**B shows the ability of the ADC v6363 to inhibit the growth of SKOV3 cells. FIG. **17**C shows the ability of the ADC v6363 to inhibit the growth of MCF7 cells. FIG. **17**D shows the ability of the ADC v6363 to inhibit the growth of MDA-MB-231 cells. FIG. **17**E shows the ability of ADCs v6363, v10553, and v1748 to inhibit the growth of SKOV3 cells. FIG. **17**F shows the ability of ADCs v6363, v10553, and v1748 to inhibit the growth of JIMT-1 cells. FIG. **17**G shows the ability of ADCs v6363, v10553, and v1748 to inhibit the growth of NCI-N87 cells.

[0025] FIG. **18** depicts the effect of a biparatopic anti-HER2 antibody in a human ovarian cancer line xenograft model (SKOV3). FIG. **18**A shows the effect of the antibody on mean tumor volume. FIG. **18**B shows the effect of the antibody on percent survival of the animals.

[0026] FIG. **19** depicts the effect of a biparatopic anti-HER2 antibody drug conjugate (ADC) in a human ovarian cancer line xenograft model (SKOV3). FIG. **19**A shows the

effect of the antibody on mean tumor volume. FIG. **19**B shows the effect of the antibody on percent survival of the animals.

[0027] FIG. **20** depicts the effect of a biparatopic anti-HER2 antibody drug conjugate (ADC) on mean tumour volume in a human breast primary cell xenograft model (HBCx-13b).

[0028] FIG. **21** depicts the effect of a biparatopic anti-HER2 antibody drug conjugate (ADC) on mean tumour volume in a human breast primary cell xenograft model (T226).

[0029] FIG. **22** depicts the effect of a biparatopic anti-HER2 antibody drug conjugate (ADC) on mean tumour volume in a human breast primary cell xenograft model (HBCx-5).

[0030] FIG. **23** depicts the effect of a biparatopic anti-HER2 antibody drug conjugate (ADC) on anti-HER2 treatment resistant tumors in a human cell line xenograft model (SKOV3).

[0031] FIG. **24** depicts the effect of a biparatopic anti-HER2 antibody drug conjugate (ADC) to anti-HER2 treatment resistant tumors in human primary cell xenograft model (HBCx-13b).

[0032] FIG. **25** depicts the thermal stability of exemplary anti-HER2 biparatopic antibodies. FIG. **25**A depicts the thermal stability of v5019. FIG. **25**B depicts the thermal stability of v10000. FIG. **25**C depicts the thermal stability of v7091.

[0033] FIG. **26** depicts the thermal stability of exemplary anti-HER2 biparatopic antibody drug conjugates. FIG. **26**A depicts the thermal stability of v6363. FIG. **26**B depicts the thermal stability of v10553. FIG. **26**C depicts the thermal stability of v7148.

[0034] FIG. **27** depicts the ability of anti-HER2 biparatopic antibodies to mediate ADCC in HER2+ cells. The legend shown in FIG. **27**C applies to FIG. **27**A and FIG. **27**B. FIG. **27**A depicts this ability in SKBR3 cells; FIG. **27**B depicts this ability in JIMT-1 cells; FIG. **27**C depicts this ability in MDA-MB-231 cells; and FIG. **27**D depicts this ability in WI-38 cells.

[0035] FIG. **28** depicts the effect of afucosylation on the ability of anti-HER2 biparatopic antibodies to mediate ADCC. The legend shown in FIG. **28**B applies to FIG. **28**A as well. FIG. **28**A compares the ability of an afucosylated version of v5019 to mediate ADCC to that of Herceptin™ in SKOV3 cells. FIG. **28**B compares the ability of an afucosylated version of v5019 to mediate ADCC to that of Herceptin™ in MDA-MB-231 cells.

[0036] FIG. **28**C compares the ability of v10000 and an afucosylated version of v10000 to mediate ADCC against that of Herceptin™ in ZR-75-1 cells.

[0037] FIG. **29** depicts the ability of v5019 to inhibit growth of BT-474 cells in the presence or absence of growth-stimulatory ligands.

[0038] FIG. **30** depicts the effect of an afucosylated version of v5019 (v7187) on tumor volume in a human breast cancer xenograft model (HBCx13B).

[0039] FIG. **31** depicts the ability of anti-HER2 biparatopic antibodies and anti-HER2 biparatopic-ADCs to bind to HER2+ tumor cells. FIG. **31**A compares the binding of v6363 to a T-DM1 analog, v6246, in SKOV3 cells. FIG. **31**B compares the binding of v6363 to a T-DM1 analog, v6246, in JIMT-1 cells. FIG. **31**C compares the binding of several exemplary anti-HER2 biparatopic antibodies and anti-HER2 biparatopic-ADCs to controls, in SKOV3 cells. FIG. **31**D compares the binding of several exemplary anti-HER2 biparatopic antibodies and anti-HER2 biparatopic-ADCs to controls, in JIMT-1 cells.

[0040] FIG. **32** depicts Dose-Dependent Tumour Growth Inhibition of an exemplary anti-HER2 biparatopic-ADC in a HER2 3+ (ER-PR negative) patient derived xenograft model (HBCx13b). FIG. **32**A shows the effect of v6363 on tumor volume, while FIG. **32**B shows the effect on percent survival.

[0041] FIG. **33** depicts the effect of Biparatopic anti-HER2-ADC v6363 compared to Standard of Care Combinations in a Trastuzumab Resistant PDX HBCx-13b xenograft model. FIG. **33**A depicts the effect of treatment on tumor volume, while FIG. **33**B depicts the effect of treatment on survival.

[0042] FIG. **34** depicts the efficacy of a biparatopic anti-HER2-ADC in HER2+ trastuzumab-resistant breast cancer cell derived tumour xenograft model (JIMT-1).

[0043] FIG. **35** depicts the efficacy of exemplary anti-HER2 biparatopic antibodies in vivo in a trastuzumab sensitive ovarian cancer cell derived tumour xenograft model (SKOV3). FIG. **35**A depicts the effect of treatment on tumor volume, while FIG. **35**B depicts the effect of treatment on survival.

[0044] FIG. **36** depicts the dose-dependent efficacy of exemplary anti-HER2 biparatopic antibodies in vivo in a trastuzumab sensitive ovarian cancer cell derived tumour xenograft model (SKOV3).

[0045] FIG. **37** depicts the ability of an anti-HER2 biparatopic antibody and an anti-HER2 biparatopic-ADC to inhibit growth of cell lines expressing HER2, and EGFR and/or HER3 at the 3+, 2+ or 1+ levels. FIG. **37**A depicts the ability of v10000 to inhibit growth selected cell lines. FIG. **37**B depicts the ability of v10553 to inhibit growth of selected cell lines.

[0046] FIG. **38** depicts a summary of the ability of v10000 and v10553 to inhibit growth in a panel of cell lines. Hyphenated values (e.g. ½) indicate discrepant erbb receptor levels as reported in the literature; Erbb IHC values were obtained internally or from the literature. Where no value is reported the receptor quantities are unknown and/or not reported. * IHC level estimate based on erBb2 gene expression data (Crown BioSciences). Numbered references are described below.

[0047] FIG. **39** depicts the ability of v10000 to mediate ADCC in HER2+ cells. FIG. **39**A depicts the results in FaDu cells. FIG. **39**B depicts the results in A549 cells. FIG. **39**C depicts the results in BxPC3 cells. FIG. **39**D depicts the results in MiaPaca2 cells.

[0048] FIG. **40** depicts the ability of anti-HER2 biparatopic antibodies to mediate ADCC in HER2+ cells. FIG. **40**A depicts the results in A549 cells. FIG. **40**B depicts the results in NCI-N87 cells. FIG. **40**C depicts the results in HCT-116 cells.

[0049] FIG. **41** depicts the effect of anti-HER2 biparatopic antibody format on binding HER2+ cells. FIG. **41**A depicts the effect of format on binding to BT-474 cells. FIG. **41**B depicts the effect of format on binding to JIMT-1 cells. FIG. **41**C depicts the effect of format on binding to MCF7 cells. FIG. **41**D depicts the effect of format on binding to MDA-MB-231 cells.

[0050] FIG. **42** depicts the effect of anti-HER2 biparatopic antibody format on internalization of antibody in HER2+

cells. FIG. **42**A depicts the effect on internalization in BT-474 cells. FIG. **42**B depicts the effect on internalization in JIMT-1 cells. FIG. **42**C depicts the effect on internalization in MCF7 cells.

[0051] FIG. **43** depicts the effect of anti-HER2 biparatopic antibody format on the ability to mediate ADCC in HER2+ cells. FIG. **43**A depicts the effect in JIMT-1 cells. FIG. **43**B depicts the effect in MCF7 cells. FIG. **43**C depicts the effect in HER2 0/1+ MDA-MB-231 breast tumor cells.

[0052] FIG. **44** depicts the effect of anti-HER2 biparatopic antibody format on the ability of the antibodies to inhibit HER2+ tumor cell growth in BT-474 cells in the presence or absence of growth-stimulatory ligands.

[0053] FIG. **45** depicts the effect of anti-HER2 biparatopic antibody format on the ability of the antibodies to inhibit growth of SKBR3 cells.

[0054] FIG. **46** depicts the effect of anti-HER2 biparatopic antibody format on the ability of antibodies to inhibit growth of HER2+ tumor cells. FIG. **46**A depicts growth inhibition in SKOV3 cells. FIG. **46**B depicts growth inhibition in JIMT-1 cells. FIG. **46**C depicts growth inhibition in MCF7 cells.

[0055] FIG. **47** depicts a comparison of binding characteristics of anti-HER2 biparatopic antibodies of differing format as measured by SPR. FIG. **47**A depicts the plot and linear regression analysis for the kd (1/s) at different antibody capture levels with v6903 and v7091. FIG. **47**B depicts the plot and linear regression analysis for the KD (M) at different antibody capture levels with v6903 and v7091.

[0056] References found in FIG. **38** are as follows: 1. Labouret et al. 2012, Neoplasia 14:121-130; 2. Ghasemi et al. 2014, Oncogenesis doi:10.1038/oncsis.2014.31; 3. Gaborit et al. 2011 J Bio Chem, 286:1133-11345; 4. Kimura et al. 2006, Clin Cancer Res; 12:4925-4932; 5. Komoto et al. 2009, Canc Sci; 101:468-473; 6. Cretella et al. 2014, Molecular Cancer 13:143-155; 7. Bunn et al. 2001, Clin Cancer Res; 7:3239-3250; 8. Lewis Phillips et al. 2013, Clin Cancer Res, 20:456-468; 9. McDonagh et al. 2012, 11:582-593; 10. Coldren et al. 2006, Mol Cancer Res: 521-528; 11. Cavazzoni et al. 2012 Mol Cancer, 11:91-115; 12. Li et al. 2014, Mol Cancer Res, doi:10.1158/1541-7786.MCR-13-0396; 13. Chmielewski et al. 2004, Immunology, 173:7647-7653; 14. Kuwada et al. 2004, Int J Cancer, 109:291-301; 15. Fujimoto-Ouchi et al. 2007, Clin Chemother Pharmacol, 59:795-805; 16. Chavez-Blanco et al. 2004, BMC Cancer, 4:59; 17. Campiglio et al. 2004, J Cellular Physiology. 198:259-268; 18. Lehmann et al. 2011, J Clin Investigation, 121:2750-2767; 19. Collins et al. 2011, Annals Oncology, 23:1788-1795; 20. Takai et al. 2005, Cancer, 104:2701-2708; 21. Rusnack et al. 2007, Cell Prolif, 40:580-594; 22. Ma et al. 2013, PLOS ONE, 8:e73261-e73261; 23. Meira et al. 2009, British J Cancer, 101:782-791; 24. Hayashi MP28-14 poster; 25. Wang et al. 2005 J Huazhong Univ Sci Technolog Med Sci. 25:326-8; 26. Makhja et al. 2010. J Clinc Oncolo 28:1215-1223.

[0057] FIG. **48**A-B depicts the effect of a biparatopic anti-HER2 antibody in a xenograft model of HER2-low, non-small cell lung cancer. FIG. **48**A shows the effect of the antibody on tumor volume. FIG. **48**B shows the effect of the antibody on percent survival of the animals.

[0058] FIG. **49**A-B depicts the effect of a biparatopic anti-HER2 antibody in a xenograft model of HER2-low, head and neck squamous cell carcinoma. FIG. **49**A shows the effect of the antibody on tumor volume. FIG. **49**B shows the effect of the antibody on percent survival of the animals.

[0059] FIG. **50**A-B depicts the effect of a biparatopic anti-HER2 antibody in a xenograft model of HER2-low, ER+ breast cancer. FIG. **50**A shows the effect of the antibody on tumor volume. FIG. **50**B shows the effect of the antibody on percent survival of the animals.

[0060] FIG. **51**A-B shows tumor volume and survival in a xenograft model of pancreatic cancer.

[0061] FIG. **52** shows tumor volume in a xenograft model of gastric cancer.

DETAILED DESCRIPTION

[0062] Described herein are methods of using bispecific antigen-binding constructs that bind HER2.

Antigen-Binding Constructs

[0063] Provided herein are antigen-binding constructs, e.g., antibodies, that bind HER2. The antigen-binding constructs include at least one antigen-binding polypeptide construct binding a HER2 ECD2 antigen. In some embodiments, antigen-binding constructs include a second antigen-binding polypeptide construct binding a second antigen, e.g., a HER2 ECD4 antigen or the HER2 ECD2 antigen. As described in more detail below, the antigen-binding polypeptide constructs can be, but are not limited to, protein constructs such as Fab (fragment antigen-binding), scFv (single chain Fv) and sdab (single domain antibody). In some embodiments, the antigen-binding construct includes a scaffold, e.g, an Fc.

[0064] The term "antigen-binding construct" refers to any agent, e.g., polypeptide or polypeptide complex capable of binding to an antigen. In some aspects an antigen-binding construct is a polypeptide that specifically binds to an antigen of interest. An antigen-binding construct can be a monomer, dimer, multimer, a protein, a peptide, or a protein or peptide complex; an antibody, an antibody fragment, or an antigen-binding fragment thereof; an scFv and the like. An antigen-binding construct can be monospecific, bispecific, or multispecific. In some aspects, an antigen-binding construct can include, e.g., one or more antigen-binding polypeptide constructs (e.g., Fabs or scFvs) linked to one or more Fc. Further examples of antigen-binding constructs are described below and provided in the Examples.

[0065] In some embodiments, the antigen-binding construct is monospecific. A monospecific antigen-binding construct refers to an antigen-binding construct with one binding specificity. In other words, the antigen-binding polypeptide construct binds to the same epitope on the same antigen. Examples of monospecific antigen-binding constructs include trastuzumab and pertuzumab.

[0066] A bispecific antigen binding construct has two antigen binding polypeptide constructs, each with a unique binding specificity. For example, a first antigen binding polypeptide construct binds to an epitope on a first antigen, and a second antigen binding polypeptide construct binds to an epitope on a second antigen. The term "biparatopic" as used herein, refers to a bispecific antibody where the first antigen binding moiety and the second antigen binding moiety bind to different epitopes on the same antigen.

[0067] An antigen-binding construct can be an antibody or antigen-binding portion thereof. As used herein, an "antibody" or "immunoglobulin" refers to a polypeptide substan-

tially encoded by an immunoglobulin gene or immunoglobulin genes, or fragments thereof, which specifically bind and recognize an analyte (e.g., antigen). The recognized immunoglobulin genes include the kappa, lambda, alpha, gamma, delta, epsilon and mu constant region genes, as well as the myriad immunoglobulin variable region genes. Light chains are classified as either kappa or lambda. The "class" of an antibody or immunoglobulin refers to the type of constant domain or constant region possessed by its heavy chain. There are five major classes of antibodies: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgG1, IgG_2, IgG_3, IgG_4, IgA1, and IgA_2. The heavy chain constant domains that correspond to the different classes of immunoglobulins are called α, δ, ϵ, γ, and respectively.

[0068] An exemplary immunoglobulin (antibody) structural unit is composed of two pairs of polypeptide chains, each pair having one "light" (about 25 kD) and one "heavy" chain (about 50-70 kD). The N-terminal domain of each chain defines a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The terms variable light chain (VL) and variable heavy chain (VH) refer to these light and heavy chain domains respectively. The IgG1 heavy chain comprises of the VH, CH1, CH2 and CH3 domains respectively from the N to C-terminus. The light chain comprises of the VL and CL domains from N to C terminus. The IgG1 heavy chain comprises a hinge between the CH1 and CH2 domains.

[0069] The term "hypervariable region" or "HVR", as used herein, refers to each of the regions of an antibody variable domain which are hypervariable in sequence and/or form structurally defined loops ("hypervariable loops"). Generally, native four-chain antibodies comprise six HVRs; three in the VH (H1, H2, H3), and three in the VL (L1, L2, L3). HVRs generally comprise amino acid residues from the hypervariable loops and/or from the complementarity determining regions (CDRs), the latter being of highest sequence variability and/or involved in antigen recognition. With the exception of CDR1 in VH, CDRs generally comprise the amino acid residues that form the hypervariable loops. Hypervariable regions (HVRs) are also referred to as "complementarity determining regions" (CDRs), and these terms are used herein interchangeably in reference to portions of the variable region that form the antigen-binding regions. This particular region has been described by Kabat et al., U.S. Dept. of Health and Human Services, Sequences of Proteins of Immunological Interest (1983) and by Chothia et al., J Mol Biol 196:901-917 (1987), where the definitions include overlapping or subsets of amino acid residues when compared against each other. Nevertheless, application of either definition to refer to a CDR of an antibody or variants thereof is intended to be within the scope of the term as defined and used herein. The exact residue numbers which encompass a particular CDR will vary depending on the sequence and size of the CDR. Those skilled in the art can routinely determine which residues comprise a particular CDR given the variable region amino acid sequence of the antibody.

[0070] "Humanized" forms of non-human (e.g., rodent) antibodies are chimeric antibodies that contain minimal sequence derived from non-human immunoglobulin. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a hypervariable region of the recipient are replaced by residues from a hypervariable region of a non-human species (donor antibody) such as mouse, rat, rabbit or nonhuman primate having the desired specificity, affinity, and capacity. In some instances, framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, humanized antibodies may comprise residues that are not found in the recipient antibody or in the donor antibody. These modifications are made to further refine antibody performance. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, 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 FRs are those of a human immunoglobulin sequence. The humanized antibody optionally also will 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); Riechmann et al., *Nature* 332:323-329 (1988); and Presta, *Curr. Op. Struct. Biol.* 2:593-596 (1992).

[0071] Humanized HER2 antibodies include huMAb4D5-1, huMAb4D5-2, huMAb4D5-3, huMAb4D5-4, huMAb4D5-5, huMAb4D5-6, huMAb4D5-7 and huMAb4D5-8 or Trastuzumab (HERCEPTIN®) as described in Table 3 of U.S. Pat. No. 5,821,337 expressly incorporated herein by reference; humanized 520C9 (WO93/21319) and humanized 2C4 antibodies as described in US Patent Publication No. 2006/0018899.

Antigen-Binding Polypeptide Construct

[0072] The antigen-binding constructs described herein comprise at least one antigen-binding polypeptide construct that each binds to a HER2 ECD2 antigen. In some embodiments, the antigen-binding constructs described herein include a second antigen-binding polypeptide construct that binds to, e.g., a HER2 ECD2 antigen or a HER2 ECD4 antigen. In some embodiments the antigen-binding polypeptide construct comprises a sequence that is disclosed in the examples below, e.g., the VH or VL or CDRs of v5019, v5020, v7091, v10000, or v6717.

[0073] The antigen-binding polypeptide construct is typically monovalent, i.e. can bind only one epitope. In some embodiments, however, the antigen-binding polypeptide construct can be bivalent (binding to two epitopes) or multivalent.

[0074] Either antigen-binding polypeptide construct can be, e.g., a Fab, or an scFv, depending on the application. In some embodiments, the antigen binding construct includes two antigen-binding polypeptide constructs. The format of the antigen-binding construct may be Fab-Fab, scFv-scFv, or Fab-scFv or scFv-Fab (first antigen-binding polypeptide construct-second antigen-binding polypeptide respectively).

[0075] A Fab (also referred to as fragment antigen-binding) contains the constant domain (CL) of the light chain and the first constant domain (CH1) of the heavy chain along with the variable domains VL and VH on the light and heavy chains respectively. The variable domains comprise the complementarity determining loops (CDR, also referred to as hypervariable region) that are involved in antigen-binding. Fab' fragments differ from Fab fragments by the addition of a few residues at the carboxy terminus of the heavy chain CH1 domain including one or more cysteines from the antibody hinge region.

[0076] A "single-chain Fv" or "scFv" includes the VH and VL domains of an antibody, wherein these domains are present in a single polypeptide chain. In one embodiment, the Fv polypeptide further comprises a polypeptide linker between the VH and VL domains which enables the scFv to form the desired structure for antigen-binding. For a review of scFv see Pluckthun in *The Pharmacology of Monoclonal Antibodies*, vol. 113, Rosenburg and Moore eds., Springer-Verlag, New York, pp. 269-315 (1994). HER2 antibody scFv fragments are described in WO93/16185; U.S. Pat. No. 5,571,894; and U.S. Pat. No. 5,587,458.

[0077] A "single domain antibody" or "sdAb" format is an individual immunoglobulin domain. SdAbs are fairly stable and easy to express as fusion partner with the Fc chain of an antibody (Harmsen MM, De Haard HJ (2007). "Properties, production, and applications of camelid single-domain antibody fragments". Appl. Microbiol Biotechnol. 77(1): 13-22).

[0078] In some embodiments the antigen binding polypeptide construct is derived from an antibody, a fibronectin, an affibody, anticalin, cysteine knot protein, DARPin, avimer, Kunitz domain or variant or derivative thereof.

[0079] The antigen binding polypeptide constructs described herein can be converted to different formats. For example, a Fab can be converted to an scFv or an scFv can be converted to a Fab. Methods of converting between types of antigen-binding domains are known in the art (see for example methods for converting an scFv to a Fab format described at, e.g., Zhou et al (2012) Mol Cancer Ther 11:1167-1476. The methods described therein are incorporated by reference.).

[0080] The antigen binding constructs described herein specifically bind HER2. "Specifically binds", "specific binding" or "selective binding" means that the binding is selective for the antigen and can be discriminated from unwanted or non-specific interactions. The ability of an antigen-binding construct to bind to a specific antigenic determinant can be measured either through an enzyme-linked immunosorbent assay (ELISA) or other techniques familiar to one of skill in the art, e.g. surface plasmon resonance (SPR) technique (analyzed on a BIAcore instrument) (Liljeblad et al, Glyco J 17, 323-329 (2000)), and traditional binding assays (Heeley, Endocr Res 28, 217-229 (2002)).

[0081] In one embodiment, the extent of binding of an antigen-binding moiety to an unrelated protein is less than about 10% of the binding of the antigen-binding construct to the antigen as measured, e.g., by SPR.

HER2

[0082] The antigen-binding constructs described herein include an antigen-binding polypeptide construct that binds to the ECD2 of HER2.

[0083] The expressions "ErbB2" and "HER2" are used interchangeably herein and refer to human HER2 protein described, for example, in Semba et al., *PNAS* (*USA*) 82:6497-6501 (1985) and Yamamoto et al. *Nature* 319:230-234 (1986) (Genebank accession number X03363). The term "erbB2" and "neu" refers to the gene encoding human ErbB2 protein. p185 or p185neu refers to the protein product of the neu gene.

[0084] HER2 is a HER receptor. A "HER receptor" is a receptor protein tyrosine kinase which belongs to the human epidermal growth factor receptor (HER) family and includes EGFR, HER2, HER3 and HER4 receptors. A HER receptor will generally comprise an extracellular domain, which may bind an HER ligand; a lipophilic transmembrane domain; a conserved intracellular tyrosine kinase domain; and a carboxyl-terminal signaling domain harboring several tyrosine residues which can be phosphorylated. By "HER ligand" is meant a polypeptide which binds to and/or activates an HER receptor.

[0085] The extracellular (ecto) domain of HER2 comprises four domains, Domain I (ECD1, amino acid residues from about 1-195), Domain II (ECD2, amino acid residues from about 196-319), Domain III (ECD3, amino acid residues from about 320-488), and Domain IV (ECD4, amino acid residues from about 489-630) (residue numbering without signal peptide). See Garrett et al. *Mol. Cell.* 11: 495-505 (2003), Cho et al. *Nature* 421: 756-760 (2003), Franklin et al. *Cancer Cell* 5:317-328 (2004), Tse et al. *Cancer Treat Rev.* 2012 April; 38(2):133-42 (2012), or Plowman et al. *Proc. Natl. Acad. Sci.* 90:1746-1750 (1993).

[0086] The sequence of HER2 is as follows; ECD boundaries are Domain I: 1-165; Domain II: 166-322; Domain III: 323-488; Domain IV: 489-607.

(SEQ ID NO: 349)

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  1   tqvctgtdmk lrlpaspeth ldmlrhlyqg cqvvqgnlel tylptnasls flgdigevqg

 61   yvliahnqvr qvplqrlriv rgtqlfedny alavldngdp lnnttpvtga spgglrelql

121   rslteilkgg vliqrnpq1c yqdtilwkdi fhknnqlalt lidtnrsrac hpcspmckgs

181   rcwgessedc qsltrtvcag gcarckgplp tdccheqcaa gctgpkhsdc laclhfnhsg

241   icelhcpalv tyntdtfesm pnpegrytfg ascvtacpyn ylstdvgsct lvcplhnqev

301   taedgtqrce kcskpcarvc yglgmehlre vravtsaniq efagckkifg slaflpesfd

361   gdpasntapl gpeqlqvfet leeitgylyi sawpdslpdl svfqnlqvir grilhngays

421   ltlqglgisw lglrslrelg sglalihhnt hlcfvhtvpw dqlfrnphqa llhtanrped

481   ecvgeglach qlcarghcwg pgptqcvncs qflrggecve ecrvlqglpr eyvnarhclp

541   chpecqpqng svtcfgpead qcvacahykd ppfcvarcps gvkpdlsymp iwkfpdeega

601   cqpcpin
```

[0087] The "epitope 2C4" is the region in the extracellular domain of HER2 to which the antibody 2C4 binds. Epitope 2C4 comprises residues from domain II in the extracellular domain of HER2. 2C4 and Pertuzumab bind to the extracellular domain of HER2 at the junction of domains I, II and III. Franklin et al. Cancer Cell 5:317-328 (2004). In order to screen for antibodies which bind to the 2C4 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. Alternatively, epitope mapping can be performed to assess whether the antibody binds to the 2C4 epitope of HER2 using methods known in the art and/or one can study the antibody-HER2 structure (Franklin et al. *Cancer Cell* 5:317-328 (2004)) to see what domain(s) of HER2 is/are bound by the antibody.

[0088] The "epitope 4D5" is the region in the extracellular domain of HER2 to which the antibody 4D5 (ATCC CRL 10463) and Trastuzumab bind. This epitope is close to the transmembrane domain of HER2, and within Domain IV of HER2. To screen for antibodies which bind to the 4D5 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. Alternatively, epitope mapping can be performed to assess whether the antibody binds to the 4D5 epitope of HER2 (e.g. any one or more residues in the region from about residue 529 to about residue 625, inclusive, see FIG. 1 of US Patent Publication No. 2006/0018899).

Exemplary Anti-HER2 Antigen Binding Constructs

[0089] Exemplary anti-HER2 antibodies (or antigen-binding constructs) and controls are provided herein. Representations of exemplary biparatopic formats are shown in FIG. **1**. In all of the formats shown in FIG. **1**, the heterodimeric Fc is depicted with one chain (Chain A) shown in black and the other (Chain B) shown in grey, while one antigen-binding domain (1) is shown in hatched fill and the other antigen-binding domain (2) is shown in white.

[0090] FIG. **1**A depicts the structure of a biparatopic antibody in a Fab-Fab format. FIGS. **1**B to **1**E depict the structure of possible versions of a biparatopic antibody in an scFv-Fab format. In FIG. **1**B, antigen-binding domain 1 is an scFv, fused to Chain A, while antigen-binding domain 2 is a Fab, fused to Chain B. In FIG. **1**C, antigen-binding domain 1 is a Fab, fused to Chain A, while antigen-binding domain 2 is an scFv, fused to Chain B. In FIG. **1**D, antigen-binding domain 2 is a Fab, fused to Chain A, while antigen-binding domain 1 is an scFv, fused to Chain B. In FIG. **1**E, antigen-binding domain 2 is an scFv, fused to Chain A, while antigen-binding domain 1 is a Fab, fused to Chain B. In FIG. **1**F, both antigen-binding domains are scFvs.

[0091] The sequences of the following variants are provided in the Sequence Table found after the Examples. CDR regions were identified using a combination of the Kabat and Chothia methods. Regions may vary slightly based on method used for identification.

[0092] Exemplary Anti-HER2 Biparatopic Antibodies

[0093] Exemplary anti-HER2 biparatopic antibodies are shown in Table 1.

TABLE 1

Exemplary anti-HER2 biparatbopic antibodies

Variant		Chain A	Chain B
5019	domain containing the epitope	ECD2	ECD4
	Format	Fab	scFv
	Antibody name	Pertuzumab	Trastuzumab
	CH3 sequence substitutions	T350V_L351Y_F405A_Y407V	T366I_N390R_K392M_T394W
5020	domain containing the epitope	ECD4	ECD2
	format	scFv	Fab
	Antibody name	Trastuzumab	Pertuzumab
	CH3 sequence substitutions	L351Y_S400E_F405A_Y407V	T350V_T366L_K392L_T394W
7091	domain containing the epitope	ECD2	ECD4
	format	Fab	scFv
	Antibody name	Pertuzumab	Trastuzumab
	CH3 sequence substitutions	T350V_L351Y_F405A_Y407V	T350V_T366L_K392L_T394W
10000	domain containing the epitope	ECD2	ECD4
	format	Fab	scFv
	Antibody name	Pertuzumab - with Y96A in VL region and T30A/A49G/L69F in VH region	Trastuzumab

TABLE 1-continued

Exemplary anti-HER2 biparatbopic antibodies

Variant		Chain A	Chain B
	CH3 sequence substitutions	T350V_L351Y_F405A_Y407V	T350V_T366L_K392L_T394W
6902	domain containing the epitope	ECD2	ECD4
	format	Fab	Fab
	Antibody name	Trastuzumab	Pertuzumab
	Fab substitutions	HC: L143E_K145T LC: Q124R	HC: D146G_Q179K LC: Q124E_Q160E_T180E
	CH3 sequence substitutions	T350V_L351Y_F405A_Y407V	T350V_T366L_K392L_T394W
6903	domain containing the epitope	ECD2	ECD4
	format	Fab	Fab
	Fab substitutions	HC: L143E_K145T LC: Q124R_Q1160K_T178R	HC: D146G_Q179K LC: Q124E_Q160E_T180E
	Antibody name	Trastuzumab	Pertuzumab
	CH3 sequence substitutions	T350V_L351Y_F405A_Y407V	T350V_T366L_K392L_T394W
6717	domain containing the epitope	ECD4	ECD2
	format	scFv	scFv
	Antibody name	Pertuzumab	Trastuzumab
	CH3 sequence substitutions	T350V_L351Y_F405A_Y407V	T366I_N390R_K392M_T394W

Notes:

CH3 numbering according to EU index as in Kabat referring to the numbering of the EU antibody (Edelman et al., 1969, Proc Natl Acad Sci USA 63: 78-85);

Fab or variable domain numbering according to Kabat (Kabat and Wu, 1991; Kabat et al, Sequences of proteins of immunological interest. 5th Edition - US Department of Health and Human Services, NIH publication n° 91-3242, p 647 (1991))

"domain containing the epitope" = domain of HER2 to which antigen-binding moiety binds;

"Antibody name" = antibody from which antigen-binding moiety is derived, includes substitutions compared to wild-type when present;

"Fab substitutions" = substitutions in Fab that promote correct light chain pairing;

"CH3 sequence substitutions" = substitutions in CH3 domain that promote formation of heterodimeric Fc

[0094] Exemplary Anti-HER2 Monovalent Control Antibodies

[0095] v1040: a monovalent anti-HER2 antibody, where the HER2 binding domain is a Fab derived from trastuzumab on chain A, and the Fc region is a heterodimer having the mutations T350V_L351Y_F405A_Y407V in Chain A, T350V_T366L_K392L_T394W in Chain B, and the hinge region of Chain B having the mutation C226S; the antigen-binding domain binds to domain 4 of HER2.

[0096] v630—a monovalent anti-HER2 antibody, where the HER2 binding domain is an scFv derived from trastuzumab on Chain A, and the Fc region is a heterodimer having the mutations L351Y_S400E_F405A_Y407V in Chain A, T366I_N390R_K392M_T394W in Chain B; and the hinge region having the mutation C226S (EU numbering) in both chains; the antigen-binding domain binds to domain 4 of HER2.

[0097] v4182: a monovalent anti-HER2 antibody, where the HER2 binding domain is a Fab derived from pertuzumab on chain A, and the Fc region is a heterodimer having the mutations T350V_L351Y_F405A_Y407V in Chain A, T350V_T366L_K392L_T394W in Chain B, and the hinge region of Chain B having the mutation C226S; the antigen-binding domain binds to domain 2 of HER2.

[0098] Exemplary Anti-HER2 Monospecific Bivalent Antibody Controls (Full-Sized Antibodies, FSAs)

[0099] v506 is a wild-type anti HER2 produced in-house in Chinese Hamster Ovary (CHO) cells, as a control. Both HER2 binding domains are derived from trastuzumab in the Fab format and the Fc is a wild type homodimer; the antigen-binding domain binds to domain 4 of HER2. This antibody is also referred to as a trastuzumab analog.

[0100] v792, is wild-type trastuzumab with a IgG1 hinge, where both HER2 binding domains are derived from trastuzumab in the Fab format, and the and the Fc region is a heterodimer having the mutations T350V_L351Y_F405A_Y407V in Chain A, and T350V_T366L_K392L_T394W Chain B; the antigen-binding domain binds to domain 4 of HER2. This antibody is also referred to as a trastuzumab analog.

[0101] v4184, a bivalent anti-HER2 antibody, where both HER2 binding domains are derived from pertuzumab in the Fab format, and the Fc region is a heterodimer having the mutations T350V_L351Y_F405A_Y407V in Chain A, and

T350V_T366L_K392L_T394W Chain B. The antigen-binding domain binds to domain 2 of HER2. This antibody is also referred to as a pertuzumab analog.

[0102] Exemplary Anti-HER2 Biparatopic Antibody Drug Conjugates (ADCs)

[0103] The following are exemplary anti-HER2 biparatopic antibody drug conjugates (anti-HER2 biparatopic-ADCs). ADCs of variants 5019, 7091, 10000 and 506 are identified as follows:

[0104] v6363 (v5019 conjugated to DM1)

[0105] v7148 (v7091 conjugated to DM1)

[0106] v10553 (v10000 conjugated to DM1)

[0107] v6246 (v506 conjugated to DM1, analogous to T-DM1, trastuzumab-emtansine)

[0108] v6249 (human IgG conjugated to DM1)

Fc of Antigen-Binding Constructs.

[0109] In some embodiments, the antigen-binding constructs described herein comprise an Fc, e.g., a dimeric Fc. A dimeric Fc can be homodimeric or heterodimeric

[0110] The term "Fc domain" or "Fc region" herein is used to define a C-terminal region of an immunoglobulin heavy chain that contains at least a portion of the constant region. The term includes native sequence Fc regions and variant Fc regions. Unless otherwise specified herein, numbering of amino acid residues in the Fc region or constant region is according to the EU numbering system, also called the EU index, as described in Kabat et al, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md., 1991. An "Fc polypeptide" of a dimeric Fc as used herein refers to one of the two polypeptides forming the dimeric Fc domain, i.e. a polypeptide comprising C-terminal constant regions of an immunoglobulin heavy chain, capable of stable self-association. For example, an Fc polypeptide of a dimeric IgG Fc comprises an IgG CH2 and an IgG CH3 constant domain sequence.

[0111] An Fc domain comprises either a CH3 domain or a CH3 and a CH2 domain. The CH3 domain comprises two CH3 sequences, one from each of the two Fc polypeptides of the dimeric Fc. The CH2 domain comprises two CH2 sequences, one from each of the two Fc polypeptides of the dimeric Fc.

[0112] In some aspects, the Fc comprises at least one or two CH3 sequences. In some aspects, the Fc is coupled, with or without one or more linkers, to a first antigen-binding construct and/or a second antigen-binding construct. In some aspects, the Fc is a human Fc. In some aspects, the Fc is a human IgG or IgG1 Fc. In some aspects, the Fc is a heterodimeric Fc. In some aspects, the Fc comprises at least one or two CH2 sequences.

[0113] In some aspects, the Fc comprises one or more modifications in at least one of the CH3 sequences. In some aspects, the Fc comprises one or more modifications in at least one of the CH2 sequences. In some aspects, an Fc is a single polypeptide. In some aspects, an Fc is multiple peptides, e.g., two polypeptides.

[0114] In some aspects, an Fc is an Fc described in patent applications PCT/CA2011/001238, filed Nov. 4, 2011 or PCT/CA2012/050780, filed Nov. 2, 2012, the entire disclosure of each of which is hereby incorporated by reference in its entirety for all purposes.

[0115] Modified CH3 Domains

[0116] In some aspects, the antigen-binding construct described herein comprises a heterodimeric Fc comprising a modified CH3 domain that has been asymmetrically modified. The heterodimeric Fc can comprise two heavy chain constant domain polypeptides: a first Fc polypeptide and a second Fc polypeptide, which can be used interchangeably provided that Fc comprises one first Fc polypeptide and one second Fc polypeptide. Generally, the first Fc polypeptide comprises a first CH3 sequence and the second Fc polypeptide comprises a second CH3 sequence.

[0117] Two CH3 sequences that comprise one or more amino acid modifications introduced in an asymmetric fashion generally results in a heterodimeric Fc, rather than a homodimer, when the two CH3 sequences dimerize. As used herein, "asymmetric amino acid modifications" refers to any modification where an amino acid at a specific position on a first CH3 sequence is different from the amino acid on a second CH3 sequence at the same position, and the first and second CH3 sequence preferentially pair to form a heterodimer, rather than a homodimer. This heterodimerization can be a result of modification of only one of the two amino acids at the same respective amino acid position on each sequence; or modification of both amino acids on each sequence at the same respective position on each of the first and second CH3 sequences. The first and second CH3 sequence of a heterodimeric Fc can comprise one or more than one asymmetric amino acid modification.

[0118] Table A provides the amino acid sequence of the human IgG1 Fc sequence, corresponding to amino acids 231 to 447 of the full-length human IgG1 heavy chain. The CH3 sequence comprises amino acid 341-447 of the full-length human IgG1 heavy chain.

[0119] Typically an Fc can include two contiguous heavy chain sequences (A and B) that are capable of dimerizing. In some aspects, one or both sequences of an Fc include one or more mutations or modifications at the following locations: L351, F405, Y407, T366, K392, T394, T350, S400, and/or N390, using EU numbering. In some aspects, an Fc includes a mutant sequence shown in Table X. In some aspects, an Fc includes the mutations of Variant 1 A-B. In some aspects, an Fc includes the mutations of Variant 2 A-B. In some aspects, an Fc includes the mutations of Variant 3 A-B. In some aspects, an Fc includes the mutations of Variant 4 A-B. In some aspects, an Fc includes the mutations of Variant 5 A-B.

TABLE A

IgG1 Fc sequences	
Human IgG1 Fc sequence 231-447 (EU-numbering)	APELLGGPSVFLFPPKPKDTLMISRTP EVTCVVVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPG K (SEQ ID NO: 350)

Variant IgG1 Fc sequence (231-447)	Chain	Mutations
1	A	L351Y_F405A_Y407V
1	B	T366L_K392M_T394W

TABLE A-continued

IgG1 Fc sequences		
2	A	L351Y_F405A_Y407V
2	B	T366L_K392L_T394W
3	A	T350V_L351Y_F405A_Y407V
3	B	T350V_T366L_K392L_T394W
4	A	T350V_L351Y_F405A_Y407V
4	B	T350V_T366L_K392M_T394W
5	A	T350V_L351Y_S400E_F405A_Y407V
5	B	T350V_T366L_N390R_K392M_T394W

[0120] The first and second CH3 sequences can comprise amino acid mutations as described herein, with reference to amino acids 231 to 447 of the full-length human IgG1 heavy chain. In one embodiment, the heterodimeric Fc comprises a modified CH3 domain with a first CH3 sequence having amino acid modifications at positions F405 and Y407, and a second CH3 sequence having amino acid modifications at position T394. In one embodiment, the heterodimeric Fc comprises a modified CH3 domain with a first CH3 sequence having one or more amino acid modifications selected from L351Y, F405A, and Y407V, and the second CH3 sequence having one or more amino acid modifications selected from T366L, T366I, K392L, K392M, and T394W.

[0121] In one embodiment, a heterodimeric Fc comprises a modified CH3 domain with a first CH3 sequence having amino acid modifications at positions L351, F405 and Y407, and a second CH3 sequence having amino acid modifications at positions T366, K392, and T394, and one of the first or second CH3 sequences further comprising amino acid modifications at position Q347, and the other CH3 sequence further comprising amino acid modification at position K360. In another embodiment, a heterodimeric Fc comprises a modified CH3 domain with a first CH3 sequence having amino acid modifications at positions L351, F405 and Y407, and a second CH3 sequence having amino acid modifications at position T366, K392, and T394, one of the first or second CH3 sequences further comprising amino acid modifications at position Q347, and the other CH3 sequence further comprising amino acid modification at position K360, and one or both of said CH3 sequences further comprise the amino acid modification T350V.

[0122] In one embodiment, a heterodimeric Fc comprises a modified CH3 domain with a first CH3 sequence having amino acid modifications at positions L351, F405 and Y407, and a second CH3 sequence having amino acid modifications at positions T366, K392, and T394 and one of said first and second CH3 sequences further comprising amino acid modification of D399R or D399K and the other CH3 sequence comprising one or more of T411E, T411D, K409E, K409D, K392E and K392D. In another embodiment, a heterodimeric Fc comprises a modified CH3 domain with a first CH3 sequence having amino acid modifications at positions L351, F405 and Y407, and a second CH3 sequence having amino acid modifications at positions T366, K392, and T394, one of said first and second CH3 sequences further comprises amino acid modification of D399R or D399K and the other CH3 sequence comprising one or more of T411E, T411D, K409E, K409D, K392E and K392D, and one or both of said CH3 sequences further comprise the amino acid modification T350V.

[0123] In one embodiment, a heterodimeric Fc comprises a modified CH3 domain with a first CH3 sequence having amino acid modifications at positions L351, F405 and Y407, and a second CH3 sequence having amino acid modifications at positions T366, K392, and T394, wherein one or both of said CH3 sequences further comprise the amino acid modification of T350V.

[0124] In one embodiment, a heterodimeric Fc comprises a modified CH3 domain comprising the following amino acid modifications, where "A" represents the amino acid modifications to the first CH3 sequence, and "B" represents the amino acid modifications to the second CH3 sequence: A:L351Y_F405A_Y407V, B:T366L_K392M_T394W, A:L351Y_F405A_Y407V, B:T366L_K392L_T394W, A:T350V_L351Y_F405A_Y407V, B:T350V_T366L_K392L_T394W, A:T350V_L351Y_F405A_Y407V, B:T350V_T366L_K392M_T394W, A:T350V_L351Y_S400E_F405A_Y407V, and/or B:T350V_T366L_N390R_K392M_T394W.

[0125] The one or more asymmetric amino acid modifications can promote the formation of a heterodimeric Fc in which the heterodimeric CH3 domain has a stability that is comparable to a wild-type homodimeric CH3 domain. In an embodiment, the one or more asymmetric amino acid modifications promote the formation of a heterodimeric Fc domain in which the heterodimeric Fc domain has a stability that is comparable to a wild-type homodimeric Fc domain. In an embodiment, the one or more asymmetric amino acid modifications promote the formation of a heterodimeric Fc domain in which the heterodimeric Fc domain has a stability observed via the melting temperature (Tm) in a differential scanning calorimetry study, and where the melting temperature is within 4° C. of that observed for the corresponding symmetric wild-type homodimeric Fc domain. In some aspects, the Fc comprises one or more modifications in at least one of the C_{H3} sequences that promote the formation of a heterodimeric Fc with stability comparable to a wild-type homodimeric Fc.

[0126] In one embodiment, the stability of the CH3 domain can be assessed by measuring the melting temperature of the CH3 domain, for example by differential scanning calorimetry (DSC). Thus, in a further embodiment, the CH3 domain has a melting temperature of about 68° C. or higher. In another embodiment, the CH3 domain has a melting temperature of about 70° C. or higher. In another embodiment, the CH3 domain has a melting temperature of about 72° C. or higher. In another embodiment, the CH3 domain has a melting temperature of about 73° C. or higher. In another embodiment, the CH3 domain has a melting temperature of about 75° C. or higher. In another embodiment, the CH3 domain has a melting temperature of about 78° C. or higher. In some aspects, the dimerized CH3 sequences have a melting temperature (Tm) of about 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 77.5, 78, 79, 80, 81, 82, 83, 84, or 85° C. or higher.

[0127] In some embodiments, a heterodimeric Fc comprising modified CH3 sequences can be formed with a purity of at least about 75% as compared to homodimeric Fc in the expressed product. In another embodiment, the heterodi-

meric Fc is formed with a purity greater than about 80%. In another embodiment, the heterodimeric Fc is formed with a purity greater than about 85%. In another embodiment, the heterodimeric Fc is formed with a purity greater than about 90%. In another embodiment, the heterodimeric Fc is formed with a purity greater than about 95%. In another embodiment, the heterodimeric Fc is formed with a purity greater than about 97%. In some aspects, the Fc is a heterodimer formed with a purity greater than about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% when expressed. In some aspects, the Fc is a heterodimer formed with a purity greater than about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% when expressed via a single cell.

[0128] Additional methods for modifying monomeric Fc polypeptides to promote heterodimeric Fc formation are described in International Patent Publication No. WO 96/027011 (knobs into holes), in Gunasekaran et al. (Gunasekaran K. et al. (2010) J Biol Chem. 285, 19637-46, electrostatic design to achieve selective heterodimerization), in Davis et al. (Davis, J H. et al. (2010) Prot Eng Des Sel; 23(4): 195-202, strand exchange engineered domain (SEED) technology), and in Labrijn et al [Efficient generation of stable bispecific IgG1 by controlled Fab-arm exchange. Labrijn A F, Meesters J I, de Goeij B E, van den Bremer E T, Neijssen J, van Kampen M D, Strumane K, Verploegen S, Kundu A, Gramer M J, van Berkel P H, van de Winkel J G, Schuurman J, Parren P W. Proc Natl Acad Sci USA. 2013 Mar. 26; 110(13):5145-50.

[0129] CH2 Domains

[0130] In some embodiments, the Fc of the antigen-binding construct comprises a CH2 domain. One example of an CH2 domain of an Fc is amino acid 231-340 of the sequence shown in Table A. Several effector functions are mediated by Fc receptors (FcRs), which bind to the Fc of an antibody.

[0131] The terms "Fc receptor" and "FcR" are used to describe a receptor that binds to the Fc region of an antibody. For example, an FcR can be a native sequence human FcR. Generally, an FcR is one which binds an IgG antibody (a gamma receptor) and includes receptors of the FcγRI, FcγRII, and FcγRIII subclasses, including allelic variants and alternatively spliced forms of these receptors. FcγRII receptors include FcγRIIA (an "activating receptor") and FcγRIIB (an "inhibiting receptor"), which have similar amino acid sequences that differ primarily in the cytoplasmic domains thereof. Immunoglobulins of other isotypes can also be bound by certain FcRs (see, e.g., Janeway et al., Immuno Biology: the immune system in health and disease, (Elsevier Science Ltd., NY) (4th ed., 1999)). Activating receptor FcγRIIA contains an immunoreceptor tyrosine-based activation motif (ITAM) in its cytoplasmic domain. Inhibiting receptor FcγRIIB contains an immunoreceptor tyrosine-based inhibition motif (ITIM) in its cytoplasmic domain (reviewed in Daeron, Annu. Rev. Immunol. 15:203-234 (1997)). FcRs are reviewed in Ravetch and Kinet, Annu. Rev. Immunol 9:457-92 (1991); Capel et al., Immunomethods 4:25-34 (1994); and de Haas et al., J. Lab. Clin. Med. 126:330-41 (1995). Other FcRs, including those to be identified in the future, are encompassed by the term "FcR" herein. The term also includes the neonatal receptor, FcRn, which is responsible for the transfer of maternal IgGs to the fetus (Guyer et al., J. Immunol. 117:587 (1976); and Kim et al., J. Immunol. 24:249 (1994)).

[0132] Modifications in the CH2 domain can affect the binding of FcRs to the Fc. A number of amino acid modifications in the Fc region are known in the art for selectively altering the affinity of the Fc for different Fcgamma receptors. In some aspects, the Fc comprises one or more modifications to promote selective binding of Fc-gamma receptors.

[0133] Exemplary mutations that alter the binding of FcRs to the Fc are listed below:

[0134] S298A/E333A/K334A, S298A/E333A/K334A/K326A (Lu Y, Vernes J M, Chiang N, et al. J Immunol Methods. 2011 Feb. 28; 365(1-2):132-41);

[0135] F243L/R292P/Y300L/V305I/P396L, F243L/R292P/Y300L/L235V/P396L (Stavenhagen J B, Gorlatov S, Tuaillon N, et al. Cancer Res. 2007 Sep. 15; 67(18):8882-90; Nordstrom J L, Gorlatov S, Zhang W, et al. Breast Cancer Res. 2011 Nov. 30; 13(6):R123);

[0136] F243L (Stewart R, Thom G, Levens M, et al. Protein Eng Des Sel. 2011 September; 24(9):671-8.), S298A/E333A/K334A (Shields R L, Namenuk A K, Hong K, et al. J Biol Chem. 2001 Mar. 2; 276(9):6591-604);

[0137] S239D/I332E/A330L, S239D/I332E (Lazar G A, Dang W, Karki S, et al. Proc Natl Acad Sci USA. 2006 Mar. 14; 103(11):4005-10);

[0138] S239D/S267E, S267E/L328F (Chu S Y, Vostiar I, Karki S, et al. Mol Immunol. 2008 September; 45(15):3926-33);

[0139] S239D/D265S/S298A/I332E, S239E/S298A/K326A/A327H, G237F/S298A/A33 0L/I332E, S239D/I332E/S298A, S239D/K326E/A330L/I332E/S298A, G236A/S239D/D270L/I3 32E, S239E/S267E/H268D, L234F/S267E/N325L, G237F/V266L/S267D and other mutations listed in WO2011/120134 and WO2011/120135, herein incorporated by reference. *Therapeutic Antibody Engineering* (by William R. Strohl and Lila M. Strohl, Woodhead Publishing series in Biomedicine No 11, ISBN 1 907568 37 9, October 2012) lists mutations on page 283.

[0140] In some embodiments an antigen-binding construct described herein comprises an antigen-binding polypeptide construct which binds an antigen; and a dimeric Fc that has superior biophysical properties like stability and ease of manufacture relative to an antigen-binding construct which does not include the same dimeric Fc. In some embodiments a CH2 domain comprises one or more asymmetric amino acid modifications. Exemplary asymmetric mutations are described in International Patent Application No. PCT/CA2014/050507.

[0141] Additional Modifications to Improve Effector Function.

[0142] In some embodiments an antigen-binding construct described herein includes modifications to improve its ability to mediate effector function. Such modifications are known in the art and include afucosylation, or engineering of the affinity of the Fc towards an activating receptor, mainly FCGR3a for ADCC, and towards C1q for CDC. The following Table B summarizes various designs reported in the literature for effector function engineering.

[0143] Methods of producing antigen-binding constructs with little or no fucose on the Fc glycosylation site (Asn 297 EU numbering) without altering the amino acid sequence are well known in the art. The GlymaX® technology (ProBioGen AG) is based on the introduction of a gene for an enzyme which deflects the cellular pathway of fucose biosynthesis into cells used for antigen-binding construct pro-

duction. This prevents the addition of the sugar "fucose" to the N-linked antibody carbohydrate part by antigen-binding construct-producing cells. (von Horsten et al. (2010) Glycobiology. 2010 December; 20 (12):1607-18. Another approach to obtaining antigen-binding constructs with lowered levels of fucosylation can be found in U.S. Pat. No. 8,409,572, which teaches selecting cell lines for antigen-binding construct production for their ability to yield lower levels of fucosylation on antigen-binding constructs Antigen-binding constructs can be fully afucosylated (meaning they contain no detectable fucose) or they can be partially afucosylated, meaning that the isolated antibody contains less than 95%, less than 85%, less than 75%, less than 65%, less than 55%, less than 45%, less than 35%, less than 25%, less than 15% or less than 5% of the amount of fucose normally detected for a similar antibody produced by a mammalian expression system.

[0144] Thus, in one embodiment, an antigen-binding construct described herein can include a dimeric Fc that comprises one or more amino acid modifications as noted in Table B that confer improved effector function. In another embodiment, the antigen-binding construct can be afucosylated to improve effector function.

TABLE B

CH2 domains and effector function engineering.

Reference	Mutations	Effect
Lu, 2011, Ferrara 2011, Mizushima 2011	Afucosylated	Increased ADCC
Lu, 2011	S298A/E333A/K334A	Increased ADCC
Lu, 2011	S298A/E333A/K334A/K326A	Increased ADCC
Stavenhagen, 2007	F243L/R292P/Y300L/V305I/P396L	Increased ADCC
Nordstrom, 2011	F243L/R292P/Y300L/L235V/P396L	Increased ADCC
Stewart, 2011	F243L	Increased ADCC
Shields, 2001	S298A/E333A/K334A	Increased ADCC
Lazar, 2006	S239D/I332E/A330L	Increased ADCC
Lazar, 2006	S239D/I332E	Increased ADCC
Bowles, 2006	AME-D, not specified mutations	Increased ADCC
Heider, 2011	37.1, mutations not disclosed	Increased ADCC
Moore, 2010	S267E/H268F/S324T	Increased CDC

[0145] Fc modifications reducing FcγR and/or complement binding and/or effector function are known in the art. Recent publications describe strategies that have been used to engineer antibodies with reduced or silenced effector activity (see Strohl, W R (2009), Curr Opin Biotech 20:685-691, and Strohl, W R and Strohl L M, "Antibody Fc engineering for optimal antibody performance" In Therapeutic Antibody Engineering, Cambridge: Woodhead Publishing (2012), pp 225-249). These strategies include reduction of effector function through modification of glycosylation, use of IgG2/IgG4 scaffolds, or the introduction of mutations in the hinge or CH2 regions of the Fc. For example, US Patent Publication No. 2011/0212087 (Strohl), International Patent Publication No. WO 2006/105338 (Xencor), US Patent Publication No. 2012/0225058 (Xencor), US Patent Publication No. 2012/0251531 (Genentech), and Strop et al ((2012) J. Mol. Biol. 420: 204-219) describe specific modifications to reduce FcγR or complement binding to the Fc.

[0146] Specific, non-limiting examples of known amino acid modifications to reduce FcγR or complement binding to the Fc include those identified in the following table:

TABLE C

modifications to reduce FcγR or complement binding to the Fc

Company	Mutations
GSK	N297A
Ortho Biotech	L234A/L235A
Protein Design labs	IGG2 V234A/G237A
Wellcome Labs	IGG4 L235A/G237A/E318A
GSK	IGG4 S228P/L236E
Alexion	IGG2/IGG4combo
Merck	IGG2 H268Q/V309L/A330S/A331S
Bristol-Myers	C220S/C226S/C229S/P238S
Seattle Genetics	C226S/C229S/E3233P/L235V/L235A
Amgen	*E. coli* production, non glyco
Medimune	L234F/L235E/P331S
Trubion	Hinge mutant, possibly C226S/P230S

[0147] In one embodiment, the Fc comprises at least one amino acid modification identified in the above table. In another embodiment the Fc comprises amino acid modification of at least one of L234, L235, or D265. In another embodiment, the Fc comprises amino acid modification at L234, L235 and D265. In another embodiment, the Fc comprises the amino acid modification L234A, L235A and D265S.

Linkers and Linker Polypeptides

[0148] In some embodiments, the antigen-binding constructs described herein include two antigen-binding polypeptide constructs. In these embodiments, the antigen-binding polypeptide constructs are each operatively linked to a linker polypeptide wherein the linker polypeptides are capable of forming a complex or interface with each other. In some embodiments, the linker polypeptides are capable of forming a covalent linkage with each other. The spatial conformation of the antigen-binding construct comprising a first and second antigen-binding polypeptide constructs with the linker polypeptides is similar to the relative spatial conformation of the paratopes of a F(ab')2 fragment generated by papain digestion, albeit in the context of an antigen-binding construct with 2 antigen-binding polypeptide constructs.

[0149] In some embodiments, the linker polypeptides are selected such that they maintain the relative spatial conformation of the paratopes of a F(ab') fragment, and are capable of forming a covalent bond equivalent to the disulphide bond in the core hinge of IgG. Suitable linker polypeptides include IgG hinge regions such as, for example those from IgG1, IgG2, or IgG4. Modified versions of these exemplary linkers can also be used. For example, modifications to improve the stability of the IgG4 hinge are known in the art (see for example, Labrijn et al. (2009) Nature Biotechnology 27, 767-771).

[0150] In one embodiment, the linker polypeptides are operatively linked to a scaffold as described here, for example an Fc. In some aspects, an Fc is coupled to the one or more antigen-binding polypeptide constructs with one or more linkers. In some aspects, Fc is coupled to the heavy chain of each antigen-binding polypeptide by a linker.

[0151] In other embodiments, the linker polypeptides are operatively linked to scaffolds other than an Fc. A number of

alternate protein or molecular domains are know in the art and can be used to form selective pairs of two different antigen-binding polypeptides. An example is the leucine zipper domains such as Fos and Jun that selectively pair together [S A Kostelny, M S Cole, and J Y Tso. Formation of a bispecific antibody by the use of leucine zippers. J Immunol 1992 148:1547-53; Bernd J. Wranik, Erin L. Christensen, Gabriele Schaefer, Janet K. Jackman, Andrew C. Vendel, and Dan Eaton. LUZ-Y, a Novel Platform for the Mammalian Cell Production of Full-length IgG-bispecific AntibodiesJ. Biol. Chem. 2012 287: 43331-43339]. Alternately, other selectively pairing molecular pairs such as the barnase barstar pair [Deyev, S. M., Waibel, R., Lebedenko, E. N., Schubiger, A. P., and Plückthun, A. (2003). Design of multivalent complexes using the barnase*barstar module. Nat Biotechnol 21, 1486-1492], DNA strand pairs [Zahida N. Chaudri, Michael Bartlet-Jones, George Panayotou, Thomas Klonisch, Ivan M. Roitt, Torben Lund, Peter J. Delves, Dual specificity antibodies using a double-stranded oligonucleotide bridge, FEBS Letters, Volume 450, Issues 1-2, 30 Apr. 1999, Pages 23-26], split fluorescent protein pairs [Ulrich Brinkmann, Alexander Haas. Fluorescent antibody fusion protein, its production and use, WO 2011135040 A1] can also be employed.

Affinity

[0152] In some embodiments, affinity is determined by SPR (surface plasmon resonance) and/or FACS (fluorescence activated cell sorting). In some embodiments, affinity is determined by SPR and/or FACS as described below.

Dissociation Constant (K) and Maximal Binding (Bmax)

[0153] In some embodiments, an antigen-binding construct is described by functional characteristics including but not limited to a dissociation constant and a maximal binding.

[0154] The term "dissociation constant (K_D)" as used herein, is intended to refer to the equilibrium dissociation constant of a particular ligand-protein interaction. As used herein, ligand-protein interactions refer to, but are not limited to protein-protein interactions or antibody-antigen interactions. The K_D measures the propensity of two proteins (e.g. AB) to dissociate reversibly into smaller components (A+B), and is define as the ratio of the rate of dissociation, also called the "off-rate (k_{off})", to the association rate, or "on-rate (k_{on})". Thus, K_D equals k_{off}/k_{on} and is expressed as a molar concentration (M). It follows that the smaller the K_D, the stronger the affinity of binding. Therefore, a K_D of 1 mM indicates weak binding affinity compared to a K_D of 1 nM. K_D values for antigen-binding constructs can be determined using methods well established in the art. One method for determining the K_D of an antigen-binding construct is by using surface plasmon resonance (SPR), typically using a biosensor system such as a Biacore® system. Isothermal titration calorimetry (ITC) is another method that can be used to determine.

[0155] The binding characteristics of an antigen-binding construct can be determined by various techniques. One of which is the measurement of binding to target cells expressing the antigen by flow cytometry (FACS, Fluorescence-activated cell sorting). Typically, in such an experiment, the target cells expressing the antigen of interest are incubated with antigen-binding constructs at different concentrations, washed, incubated with a secondary agent for detecting the antigen-binding construct, washed, and analyzed in the flow cytometer to measure the median fluorescent intensity (MFI) representing the strength of detection signal on the cells, which in turn is related to the number of antigen-binding constructs bound to the cells. The antigen-binding construct concentration vs. MFI data is then fitted into a saturation binding equation to yield two key binding parameters, Bmax and apparent K_D.

[0156] Apparent K_D, or apparent equilibrium dissociation constant, represents the antigen-binding construct concentration at which half maximal cell binding is observed. Evidently, the smaller the K_D value, the smaller antigen-binding construct concentration is required to reach maximum cell binding and thus the higher is the affinity of the antigen-binding construct. The apparent K_D is dependent on the conditions of the cell binding experiment, such as different receptor levels expressed on the cells and incubation conditions, and thus the apparent K_D is generally different from the K_D values determined from cell-free molecular experiments such as SPR and ITC. However, there is generally good agreement between the different methods.

[0157] The term "Bmax", or maximal binding, refers to the maximum antigen-binding construct binding level on the cells at saturating concentrations of antigen-binding construct. This parameter can be reported in the arbitrary unit MFI for relative comparison, or converted into an absolute value corresponding to the number of antigen-binding constructs bound to the cell with the use of a standard curve.

Testing of Antigen-Binding Constructs: HER2 Binding

[0158] The antigen-binding constructs or pharmaceutical compositions described herein are tested in vitro, and then in vivo for the desired therapeutic or prophylactic activity, prior to use in humans. For example, in vitro assays to demonstrate the therapeutic or prophylactic utility of a compound or pharmaceutical composition include, the effect of a compound on a cell line or a patient tissue sample. The effect of the compound or composition on the cell line and/or tissue sample can be determined utilizing techniques known to those of skill in the art including, but not limited to, rosette formation assays and cell lysis assays. In accordance with the invention, in vitro assays which can be used to determine whether administration of a specific antigen-binding construct is indicated, include in vitro cell culture assays, or in vitro assays in which a patient tissue sample is grown in culture, and exposed to or otherwise administered antigen-binding construct, and the effect of such antigen-binding construct upon the tissue sample is observed.

[0159] Candidate antigen-binding constructs can be assayed using cells, e.g., breast cancer cell lines, expressing HER2. The following Table D describes the expression level of HER2 in several representative cancer cell lines.

TABLE D

Relative expression levels of HER2 in cell lines of interest.

Cell Line	Description	IHC scoring	HER2 receptors/cell
NCI-N87	Human gastric carcinoma	3+	Not assessed
A549	Human lung alveolar carcinoma (non-small cell lung cancer)	0/1+	Not assessed

TABLE D-continued

Relative expression levels of HER2 in cell lines of interest.

Cell Line	Description	IHC scoring	HER2 receptors/cell
BxPC-3	Human pancreatic adenocarcinoma	1+	Not assessed
MIA PaCa-2	Human pancreatic ductal adenocarcinoma	2+	Not assessed
FaDu	Human pharyngeal squamous cell carcinoma	2+	Not assessed
HCT-116	Human colorectal epithelial carcinoma	1+	Not assessed
WI-38	Normal fetal lung	0	1.0 × 10E4
MDA-MB-231	Human triple negative breast epithelial adenocarcinoma	0/1+	1.7 × 10E4-2.3 × 10E4
MCF-7	Human estrogen receptor positive breast epithelial adenocarcinoma	1+	4 × 10E4-7 × 10E4
JIMT-1	Trastuzumab resistant breast epithelial carcinoma, amplified HER2 oncogene, insensitive to HER2-inhibiting drugs (i.e. Herceptin ™)	2+	2 × 10E5-8 × 10E5
ZR-75-1	Estrogen receptor positive breast ductal carcinoma	2+	3 × 10E5
SKOV-3	Human ovarian epithelial adenocarcinoma, HER2 gene amplified	2/3+	5 × 10E5-1 × 10E6
SK-BR-3	Human breast epithelial adenocarcinoma	3+	>1 × 10E6
BT-474	Human breast epithelial ductal carcinoma,	3+	>1 × 10E6

[0160] McDonagh et al Mol Cancer Ther. 2012 March; 11(3):582-93; Subik et al. (2010) Breast Cancer: Basic Clinical Research: 4; 35-41; Carter et al. PNAS, 1994:89; 4285-4289; Yarden 2000, HER2: Basic Research, Prognosis and Therapy; Hendricks et al Mol Cancer Ther 2013; 12:1816-28.

[0161] As is known in the art, a number of assays may be employed in order to identify antigen-binding constructs suitable for use in the methods described herein. These assays can be carried out in cancer cells expressing HER2. Examples of suitable cancer cells are identified in Table A5. Examples of assays that may be carried out are described as follows.

[0162] For example, to identify growth inhibitory candidate antigen-binding constructs that bind HER2, one may screen for antibodies which inhibit the growth of cancer cells which express HER2. In one embodiment, the candidate antigen-binding construct of choice is able to inhibit growth of cancer cells in cell culture by about 20-100% and preferably by about 50-100% at compared to a control antigen-binding construct.

[0163] To select for candidate antigen-binding constructs which induce cell death, loss of membrane integrity as indicated by, e.g., PI (phosphatidylinositol), trypan blue or 7AAD uptake may be assessed relative to control.

[0164] In order to select for candidate antigen-binding constructs which induce apoptosis, an annexin binding assay may be employed. In addition to the annexin binding assay, a DNA staining assay may also be used.

[0165] In one embodiment, the candidate antigen-binding construct of interest may block heregulin dependent association of ErbB2 with ErbB3 in both MCF7 and SK-BR-3 cells as determined in a co-immunoprecipitation experiment substantially more effectively than monoclonal antibody 4D5, and preferably substantially more effectively than monoclonal antibody 7F3.

[0166] To screen for antigen-binding constructs which bind to an epitope on ErbB2 bound by an antibody of interest, 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. Alternatively, or additionally, epitope mapping can be performed by methods known in the art.

[0167] Competition between antigen-binding constructs can be determined by an assay in which an antigen-binding construct under test inhibits or blocks specific binding of a reference antigen-binding construct to a common antigen (see, e.g., Junghans et al., Cancer Res. 50:1495, 1990; Fendly et al. Cancer Research 50: 1550-1558; U.S. Pat. No. 6,949,245). A test antigen-binding construct competes with a reference antigen-binding construct if an excess of a test antigen-binding construct (e.g., at least 2×, 5×, 10×, 20×, or 100×) inhibits or blocks binding of the reference antigen-binding construct by, e.g., at least 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% as measured in a competitive binding assay. Antigen-binding constructs identified by competition assay (competing antigen-binding construct) include antigen-binding constructs binding to the same epitope as the reference antigen-binding construct and antigen-binding constructs binding to an adjacent epitope sufficiently proximal to the epitope bound by the reference antigen-binding construct for steric hindrance to occur. For example, a second, competing antigen-binding construct can be identified that competes for binding to HER2 with a first antigen-binding construct described herein. In certain instances, the second construct can block or inhibit binding of the first construct by, e.g., at least 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% as measured in a competitive binding assay. In certain instances, the second construct can displace the first construct by greater than 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, or 99%.

[0168] In some embodiments, antigen-binding constructs described herein are assayed for function in vivo, e.g., in animal models. In some embodiments, the animal models are those described in Table E. In some embodiments, the animal models are those described in the Examples. In some embodiments, the antigen-binding constructs display an increase in efficacy of treatment in an animal model compared to a reference antigen-binding construct.

TABLE E

Animal models for testing HER2 binding antigen-binding constructs

Xenograft Model	Description	Reference
SKOV3 human ovarian cancer	HER2+/3+, gene amplified, moderately sensitive to trastuzumab	Rhodes et al. 2002. American Journal of Pathology 118: 408-417; Sims et al. 2012. British Journal of Cancer 106: 1779-1789
HBCx-13b human metastatic breast cancer	HER2 3+, estrogen receptor negative, progesterone receptor negative; Invasive ductal breast carcinoma; Chemotherapy resistant, Trastuzumab resistant	Marangoni et al. 2007. Clinical Cancer Research 13: 3989-3998; Reyal et al. 2012. Breast Cancer Research 14: R11
T226 human breast cancer	HER2 3+, estrogen receptor negative, progesterone receptor negative; Inflammatory breast cancer; Trastuzumab resistant, Docetaxel and capecitabine moderately sensitive, Adriamycin/cyclophosphamide sensitive	
HBCx-5 human breast cancer	HER2 3+, estrogen receptor negative, progesterone receptor negative; Invasive ductal carcinoma, luminal B; Trastuzumab resistant, Docetaxel moderately sensitive, Capecitabine, Adriamycin/Cyclophosphamide sensitive	Marangoni et al. 2007. Clinical Cancer Research 13: 3989-3998; Reyal et al. 2012. Breast Cancer Research 14: R11
JIMT-1 human breast cancer	HER2 2+, HER2 gene amplified, Trastuzumab and pertuzumab resistant	Tanner et al. 2004. Molecular Cancer Therapeutics 3: 1585-1592

Reference Antigen-Binding Construct

[0169] In some embodiments, the functional characteristics of the antigen-binding constructs described herein are compared to those of a reference antigen-binding construct. The identity of the reference antigen-binding construct depends on the functional characteristic being measured or the distinction being made. For example, when comparing the functional characteristics of antigen-binding constructs described herein, the reference antigen-binding construct may be a trastuzumab (for example v6336), or analog thereof, or may be a control IgG, for example a non-specific polyclonal human antibody.

Antigen-Binding Constructs and Antibody Drug Conjugates (ADC)

[0170] In certain embodiments an antigen-binding construct is conjugated to a drug, e.g., a toxin, a chemotherapeutic agent, an immune modulator, or a radioisotope. Several methods of preparing ADCs (antibody drug conjugates or antigen-binding construct drug conjugates) are known in the art and are described below.

[0171] In some embodiments, the drug is selected from a maytansine, auristatin, calicheamicin, or derivative thereof. In other embodiments, the drug is a maytansine selected from DM1 and DM4. Further examples are described below.

[0172] In some embodiments the drug is conjugated to the isolated antigen-binding construct with an SMCC linker (DM1), or an SPDB linker (DM4). Additional examples are described below. The drug-to-antigen-binding protein ratio (DAR) can be, e.g., 1.0 to 6.0 or 3.0 to 5.0 or 3.5-4.2.

[0173] In some embodiments the antigen-binding construct is conjugated to a cytotoxic agent. The term "cytotoxic agent" as used herein refers to a substance that inhibits or prevents the function of cells and/or causes destruction of cells. The term is intended to include radioactive isotopes (e.g. At211, I131, I125, Y90, Re186, Re188, Sm153, Bi212, P32, and Lu177), chemotherapeutic agents, and toxins such as small molecule toxins or enzymatically active toxins of bacterial, fungal, plant or animal origin, including fragments and/or variants thereof. Further examples are described below.

[0174] Drugs

[0175] Non-limiting examples of drugs or payloads used in various embodiments of ADCs include DM1 (maytansine, N2'-deacetyl-N2'-(3-mercapto-1-oxopropyl)- or N2'-deacetyl-N2'-(3-mercapto-1-oxopropyl)-maytansine), mc-MMAD (6-maleimidocaproyl-monomethylauristatin-D or N-methyl-L-valyl-N-[(1S,2R)-2-methoxy-4-[(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-[[(1S)-2-phenyl-1-(2-thiazolyl)ethyl]amino]propyl]-1-pyrrolidinyl]-1-[(1S)-1-methylpropyl]-4-oxobutyl]-N-methyl-(9Cl)-L-valinamide), mc-MMAF (maleimidocaproyl-monomethylauristatin F or N-[6-(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)-1-oxohexyl]-N-methyl-L-valyl-L-valyl-(3R,4S,5S)-3-methoxy-5-methyl-4-(methylamino)heptanoyl-(αR, βR,2S)-β-methoxy-α-methyl-2-pyrrolidinepropanoyl-L-phenylalanine) and mc-Val-Cit-PABA-MMAE (6-maleimidocaproyl-ValcCit-(p-aminobenzyloxycarbonyl)-monomethylauristatin E or N-[[[4-[[N-[6-(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)-1-oxohexyl]-L-valyl-N5-(aminocarbonyl)-L-ornithyl]amino]phenyl]methoxy]carbonyl]-N-methyl-L-valyl-N-[(1S,2R)-4-[(2S)-2-[(1R,2R)-3-[[(1R,2S)-2-hydroxy-1-methyl-2-phenylethyl]amino]-1-methoxy-2-methyl-3-oxopropyl]-1-pyrrolidinyl]-2-methoxy-1-[(1S)-1-methylpropyl]-4-oxobutyl]-N-methyl-L-valinamide). DM1 is a derivative of the tubulin inhibitor maytansine while MMAD, MMAE, and MMAF are auristatin derivatives.

[0176] Maytansinoid Drug Moieties

[0177] As indicated above, in some embodiments the drug is a maytansinoid. Exemplary maytansinoids include DM1, DM3 ($N^{2'}$-deacetyl-$N^{2'}$-(4-mercapto-1-oxopentyl) may-

tansine), and DM4 ($N^{2'}$-deacetyl-$N^{2'}$-(4-methyl-4-mercapto-1-oxopentyl)methylmaytansine) (see US20090202536).

[0178] Many positions on maytansine compounds are known to be useful as the linkage position, depending upon the type of link. For example, for forming an ester linkage, the C-3 position having a hydroxyl group, the C-14 position modified with hydroxymethyl, the C-15 position modified with a hydroxyl group and the C-20 position having a hydroxyl group are all suitable.

[0179] All stereoisomers of the maytansinoid drug moiety are contemplated for the ADCs described herein, i.e. any combination of R and S configurations at the chiral carbons of D.

[0180] Auristatins

[0181] In some embodiments, the drug is an auristatin, such as auristatin E (also known in the art as a derivative of dolastatin-10) or a derivative thereof. The auristatin can be, for example, an ester formed between auristatin E and a keto acid. For example, auristatin E can be reacted with paraacetyl benzoic acid or benzoylvaleric acid to produce AEB and AEVB, respectively. Other typical auristatins include AFP, MMAF, and MMAE. The synthesis and structure of exemplary auristatins are described in U.S. Pat. Nos. 6,884,869, 7,098,308, 7,256,257, 7,423,116, 7,498,298 and 7,745,394, each of which is incorporated by reference herein in its entirety and for all purposes.

[0182] Chemotherapeutic Agents

[0183] In some embodiments the antigen-binding construct is conjugated to a chemotherapeutic agent. Examples include but are not limited to Cisplantin and Lapatinib. A "chemotherapeutic agent" is a chemical compound useful in the treatment of cancer.

[0184] Examples of chemotherapeutic agents include alkylating agents such as thiotepa and cyclosphosphamide (CYTOXAN™); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethylenethiophosphaoramide and trimethylolomelamine; nitrogen mustards such as chlorambucil, chlomaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine; antibiotics such as aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, calicheamicin, carabicin, carminomycin, carzinophilin, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, 5-FU; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfornithine; elliptinium acetate; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidamine; mitoguazone; mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK7; razoxane; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2'=-trichlorotriethylamine; urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxanes, e.g. paclitaxel (TAXOL®, Bristol-Myers Squibb Oncology, Princeton, N.J.) and doxetaxel (TAXOTERE®, Rhone-Poulenc Rorer, Antony, France); chlorambucil; gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitomycin C; mitoxantrone; vincristine; vinorelbine; navelbine; novantrone; teniposide; daunomycin; aminopterin; xeloda; ibandronate; CPT-11; topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoic acid; esperamicins; capecitabine; and pharmaceutically acceptable salts, acids or derivatives of any of the above. Also included in this definition are anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens including for example tamoxifen, raloxifene, aromatase inhibiting 4(5)-imidazoles, 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone, and toremifene (Fareston); and anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; and pharmaceutically acceptable salts, acids or derivatives of any of the above.

[0185] Conjugate Linkers

[0186] In some embodiments, the drug is linked to the antigen-binding construct, e.g., antibody, by a linker. Attachment of a linker to an antibody can be accomplished in a variety of ways, such as through surface lysines, reductive-coupling to oxidized carbohydrates, and through cysteine residues liberated by reducing interchain disulfide linkages. A variety of ADC linkage systems are known in the art, including hydrazone-, disulfide- and peptide-based linkages.

[0187] Suitable linkers include, for example, cleavable and non-cleavable linkers. A cleavable linker is typically susceptible to cleavage under intracellular conditions. Suitable cleavable linkers include, for example, a peptide linker cleavable by an intracellular protease, such as lysosomal protease or an endosomal protease. In exemplary embodiments, the linker can be a dipeptide linker, such as a valine-citrulline (val-cit), a phenylalanine-lysine (phe-lys) linker, or maleimidocapronic-valine-citruline-p-aminobenzyloxycarbonyl (mc-Val-Cit-PABA) linker. Another linker is Sulfosuccinimidyl-4-[N-maleimidomethyl]cyclohexane-1-carboxylate (SMCC). Sulfo-smcc conjugation occurs via a maleimide group which reacts with sulfhydryls (thiols, —SH), while its Sulfo-NHS ester is reactive toward primary amines (as found in Lysine and the protein or peptide N-terminus). Yet another linker is maleimidocaproyl (MC). Other suitable linkers include linkers hydrolyzable at a specific pH or a pH range, such as a hydrazone linker. Additional suitable cleavable linkers include disulfide linkers. The linker may be covalently bound to the antibody to such an extent that the antibody must be degraded intracellularly in order for the drug to be released e.g. the MC linker and the like.

[0188] Preparation of ADCs

[0189] The ADC may be prepared by several routes, employing organic chemistry reactions, conditions, and reagents known to those skilled in the art, including: (1) reaction of a nucleophilic group or an electrophilic group of an antibody with a bivalent linker reagent, to form antibody-linker intermediate Ab-L, via a covalent bond, followed by reaction with an activated drug moiety D; and (2) reaction of a nucleophilic group or an electrophilic group of a drug moiety with a linker reagent, to form drug-linker intermediate D-L, via a covalent bond, followed by reaction with the nucleophilic group or an electrophilic group of an antibody. Conjugation methods (1) and (2) may be employed with a variety of antibodies, drug moieties, and linkers to prepare the antibody-drug conjugates described here.

[0190] Several specific examples of methods of preparing ADCs are known in the art and are described in U.S. Pat. No. 8,624,003 (pot method), U.S. Pat. No. 8,163,888 (one-step), and U.S. Pat. No. 5,208,020 (two-step method).

Methods of Preparation of Antigen-Binding Constructs

[0191] Antigen-binding constructs described herein may be produced using recombinant methods and compositions, e.g., as described in U.S. Pat. No. 4,816,567.

[0192] In one embodiment, isolated nucleic acid encoding an antigen-binding construct described herein is provided. Such nucleic acid may encode an amino acid sequence comprising the VL and/or an amino acid sequence comprising the VH of the antigen-binding construct (e.g., the light and/or heavy chains of the antigen-binding construct). In a further embodiment, one or more vectors (e.g., expression vectors) comprising such nucleic acid are provided. In one embodiment, the nucleic acid is provided in a multicistronic vector. In a further embodiment, a host cell comprising such nucleic acid is provided. In one such embodiment, a host cell comprises (e.g., has been transformed with): (1) a vector comprising a nucleic acid that encodes an amino acid sequence comprising the VL of the antigen-binding construct and an amino acid sequence comprising the VH of the antigen-binding polypeptide construct, or (2) a first vector comprising a nucleic acid that encodes an amino acid sequence comprising the VL of the antigen-binding polypeptide construct and a second vector comprising a nucleic acid that encodes an amino acid sequence comprising the VH of the antigen-binding polypeptide construct. In one embodiment, the host cell is eukaryotic, e.g. a Chinese Hamster Ovary (CHO) cell, or human embryonic kidney (HEK) cell, or lymphoid cell (e.g., Y0, NS0, Sp20 cell). In one embodiment, a method of making an antigen-binding construct is provided, wherein the method comprises culturing a host cell comprising nucleic acid encoding the antigen-binding construct, as provided above, under conditions suitable for expression of the antigen-binding construct, and optionally recovering the antigen-binding construct from the host cell (or host cell culture medium).

[0193] For recombinant production of the antigen-binding construct, nucleic acid encoding an antigen-binding construct, e.g., as described above, is isolated and inserted into one or more vectors for further cloning and/or expression in a host cell. Such nucleic acid may be readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the antigen-binding construct).

[0194] The term "substantially purified" refers to a construct described herein, or variant thereof that may be substantially or essentially free of components that normally accompany or interact with the protein as found in its naturally occurring environment, i.e. a native cell, or host cell in the case of recombinantly produced heteromultimer that in certain embodiments, is substantially free of cellular material includes preparations of protein having less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, less than about 4%, less than about 3%, less than about 2%, or less than about 1% (by dry weight) of contaminating protein. When the heteromultimer or variant thereof is recombinantly produced by the host cells, the protein in certain embodiments is present at about 30%, about 25%, about 20%, about 15%, about 10%, about 5%, about 4%, about 3%, about 2%, or about 1% or less of the dry weight of the cells. When the heteromultimer or variant thereof is recombinantly produced by the host cells, the protein, in certain embodiments, is present in the culture medium at about 5 g/L, about 4 g/L, about 3 g/L, about 2 g/L, about 1 g/L, about 750 mg/L, about 500 mg/L, about 250 mg/L, about 100 mg/L, about 50 mg/L, about 10 mg/L, or about 1 mg/L or less of the dry weight of the cells. In certain embodiments, "substantially purified" heteromultimer produced by the methods described herein, has a purity level of at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, specifically, a purity level of at least about 75%, 80%, 85%, and more specifically, a purity level of at least about 90%, a purity level of at least about 95%, a purity level of at least about 99% or greater as determined by appropriate methods such as SDS/PAGE analysis, RP-HPLC, SEC, and capillary electrophoresis.

[0195] Suitable host cells for cloning or expression of antigen-binding construct-encoding vectors include prokaryotic or eukaryotic cells described herein.

[0196] A "recombinant host cell" or "host cell" refers to a cell that includes an exogenous polynucleotide, regardless of the method used for insertion, for example, direct uptake, transduction, f-mating, or other methods known in the art to create recombinant host cells. The exogenous polynucleotide may be maintained as a nonintegrated vector, for example, a plasmid, or alternatively, may be integrated into the host genome.

[0197] As used herein, the term "eukaryote" refers to organisms belonging to the phylogenetic domain Eucarya such as animals (including but not limited to, mammals, insects, reptiles, birds, etc.), ciliates, plants (including but not limited to, monocots, dicots, algae, etc.), fungi, yeasts, flagellates, microsporidia, protists, etc.

[0198] As used herein, the term "prokaryote" refers to prokaryotic organisms. For example, a non-eukaryotic organism can belong to the Eubacteria (including but not limited to, *Escherichia coli, Thermus thermophilus, Bacillus stearothermophilus, Pseudomonas fluorescens, Pseudomonas aeruginosa, Pseudomonas putida*, etc.) phylogenetic domain, or the Archaea (including but not limited to, *Methanococcus jannaschii, Methanobacterium thermoautotrophicum, Halobacterium* such as *Haloferax volcanii* and *Halobacterium* species NRC-1, *Archaeoglobus fulgidus, Pyrococcus furiosus, Pyrococcus horikoshii, Aeuropyrum pemix*, etc.) phylogenetic domain.

[0199] For example, antigen-binding construct may be produced in bacteria, in particular when glycosylation and Fc effector function are not needed. For expression of antigen-binding construct fragments and polypeptides in bacteria, see, e.g., U.S. Pat. Nos. 5,648,237, 5,789,199, and 5,840,523. (See also Charlton, *Methods in Molecular Biology*, Vol. 248 (B.K.C. Lo, ed., Humana Press, Totowa, N.J., 2003), pp. 245-254, describing expression of antibody fragments in *E. coli*.) After expression, the antigen-binding construct may be isolated from the bacterial cell paste in a soluble fraction and can be further purified.

[0200] In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for antigen-binding construct-encoding vectors, including fungi and yeast strains whose glycosylation pathways have been "humanized," resulting in the production of an antigen-binding construct with a partially or fully human glycosylation pattern. See Gerngross, *Nat. Biotech.* 22:1409-1414 (2004), and Li et al., *Nat. Biotech.* 24:210-215 (2006).

[0201] Suitable host cells for the expression of glycosylated antigen-binding constructs are also derived from multicellular organisms (invertebrates and vertebrates). Examples of invertebrate cells include plant and insect cells. Numerous baculoviral strains have been identified which may be used in conjunction with insect cells, particularly for transfection of *Spodoptera frugiperda* cells.

[0202] Plant cell cultures can also be utilized as hosts. See, e.g., U.S. Pat. Nos. 5,959,177, 6,040,498, 6,420,548, 7,125,978, and 6,417,429 (describing PLANTIBODIES™ technology for producing antigen-binding constructs in transgenic plants).

[0203] Vertebrate cells may also be used as hosts. For example, mammalian cell lines that are adapted to grow in suspension may be useful. Other examples of useful mammalian host cell lines are monkey kidney CV1 line transformed by SV40 (COS-7); human embryonic kidney line (293 or 293 cells as described, e.g., in Graham et al., *J Gen Virol.* 36:59 (1977)); baby hamster kidney cells (BHK); mouse sertoli cells (TM4 cells as described, e.g., in Mather, *Biol. Reprod.* 23:243-251 (1980)); monkey kidney cells (CV1); African green monkey kidney cells (VERO-76); human cervical carcinoma cells (HELA); canine kidney cells (MDCK; buffalo rat liver cells (BRL 3A); human lung cells (W138); human liver cells (Hep G2); mouse mammary tumor (MMT 060562); TRI cells, as described, e.g., in Mather et al., *Annals N.Y. Acad. Sci.* 383:44-68 (1982); MRC 5 cells; and FS4 cells. Other useful mammalian host cell lines include Chinese hamster ovary (CHO) cells, including DHFR CHO cells (Urlaub et al., *Proc. Natl. Acad. Sci. USA* 77:4216 (1980)); and myeloma cell lines such as Y0, NS0 and Sp2/0. For a review of certain mammalian host cell lines suitable for antigen-binding construct production, see, e.g., Yazaki and Wu, *Methods in Molecular Biology*, Vol. 248 (B.K.C. Lo, ed., Humana Press, Totowa, N.J.), pp. 255-268 (2003).

[0204] In one embodiment, the antigen-binding constructs described herein are produced in stable mammalian cells, by a method comprising: transfecting at least one stable mammalian cell with: nucleic acid encoding the antigen-binding construct, in a predetermined ratio; and expressing the nucleic acid in the at least one mammalian cell. In some embodiments, the predetermined ratio of nucleic acid is determined in transient transfection experiments to determine the relative ratio of input nucleic acids that results in the highest percentage of the antigen-binding construct in the expressed product.

[0205] In some embodiments is the method of producing a antigen-binding construct in stable mammalian cells as described herein wherein the expression product of the at least one stable mammalian cell comprises a larger percentage of the desired glycosylated antigen-binding construct as compared to the monomeric heavy or light chain polypeptides, or other antibodies.

[0206] In some embodiments is the method of producing a glycosylated antigen-binding construct in stable mammalian cells described herein, said method comprising identifying and purifying the desired glycosylated antigen-binding construct. In some embodiments, the said identification is by one or both of liquid chromatography and mass spectrometry.

[0207] If required, the antigen-binding constructs can be purified or isolated after expression. Proteins may be isolated or purified in a variety of ways known to those skilled in the art. Standard purification methods include chromatographic techniques, including ion exchange, hydrophobic interaction, affinity, sizing or gel filtration, and reversed-phase, carried out at atmospheric pressure or at high pressure using systems such as FPLC and HPLC. Purification methods also include electrophoretic, immunological, precipitation, dialysis, and chromatofocusing techniques. Ultrafiltration and diafiltration techniques, in conjunction with protein concentration, are also useful. As is well known in the art, a variety of natural proteins bind Fc and antibodies, and these proteins can find use in the present invention for purification of antigen-binding constructs. For example, the bacterial proteins A and G bind to the Fc region. Likewise, the bacterial protein L binds to the Fab region of some antibodies. Purification can often be enabled by a particular fusion partner. For example, antibodies may be purified using glutathione resin if a GST fusion is employed, Ni^{+2} affinity chromatography if a His-tag is employed, or immobilized anti-flag antibody if a flag-tag is used. For general guidance in suitable purification techniques, see, e.g. incorporated entirely by reference Protein Purification: Principles and Practice, 3rd Ed., Scopes, Springer-Verlag, N.Y., 1994, incorporated entirely by reference. The degree of purification necessary will vary depending on the use of the antigen-binding constructs. In some instances no purification is necessary.

[0208] In certain embodiments the antigen-binding constructs are purified using Anion Exchange Chromatography including, but not limited to, chromatography on Q-sepharose, DEAE sepharose, poros HQ, poros DEAF, Toyopearl Q, Toyopearl QAE, Toyopearl DEAE, Resource/Source Q and DEAE, Fractogel Q and DEAE columns.

[0209] In specific embodiments the proteins described herein are purified using Cation Exchange Chromatography including, but not limited to, SP-sepharose, CM sepharose, poros HS, poros CM, Toyopearl SP, Toyopearl CM, Resource/Source S and CM, Fractogel S and CM columns and their equivalents and comparables.

[0210] In addition, antigen-binding constructs described herein can be chemically synthesized using techniques known in the art (e.g., see Creighton, 1983, Proteins: Structures and Molecular Principles, W. H. Freeman & Co., N.Y and Hunkapiller et al., Nature, 310:105-111 (1984)). For example, a polypeptide corresponding to a fragment of a

polypeptide can be synthesized by use of a peptide synthesizer. Furthermore, if desired, nonclassical amino acids or chemical amino acid analogs can be introduced as a substitution or addition into the polypeptide sequence. Nonclassical amino acids include, but are not limited to, to the D-isomers of the common amino acids, 2,4diaminobutyric acid, alpha-amino isobutyric acid, 4aminobutyric acid, Abu, 2-amino butyric acid, g-Abu, e-Ahx, 6amino hexanoic acid, Aib, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosine, citrulline, homocitrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, □-alanine, fluoro-amino acids, designer amino acids such as □-methyl amino acids, C□-methyl amino acids, N□-methyl amino acids, and amino acid analogs in general. Furthermore, the amino acid can be D (dextrorotary) or L (levorotary).

[0211] Post-Translational Modifications:

[0212] In certain embodiments antigen-binding constructs described herein are differentially modified during or after translation.

[0213] The term "modified," as used herein refers to any changes made to a given polypeptide, such as changes to the length of the polypeptide, the amino acid sequence, chemical structure, co-translational modification, or post-translational modification of a polypeptide. The form "(modified)" term means that the polypeptides being discussed are optionally modified, that is, the polypeptides under discussion can be modified or unmodified.

[0214] The term "post-translationally modified" refers to any modification of a natural or non-natural amino acid that occurs to such an amino acid after it has been incorporated into a polypeptide chain. The term encompasses, by way of example only, co-translational in vivo modifications, co-translational in vitro modifications (such as in a cell-free translation system), post-translational in vivo modifications, and post-translational in vitro modifications.

[0215] In some embodiments, the modification is at least one of: glycosylation, acetylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage and linkage to an antibody molecule or antigen-binding construct or other cellular ligand. In some embodiments, the antigen-binding construct is chemically modified by known techniques, including but not limited, to specific chemical cleavage by cyanogen bromide, trypsin, chymotrypsin, papain, V8 protease, $NaBH_4$; acetylation, formylation, oxidation, reduction; and metabolic synthesis in the presence of tunicamycin.

[0216] Additional post-translational modifications of antigen-binding constructs described herein include, for example, N-linked or O-linked carbohydrate chains, processing of N-terminal or C-terminal ends), attachment of chemical moieties to the amino acid backbone, chemical modifications of N-linked or O-linked carbohydrate chains, and addition or deletion of an N-terminal methionine residue as a result of procaryotic host cell expression. The antigen-binding constructs described herein are modified with a detectable label, such as an enzymatic, fluorescent, isotopic or affinity label to allow for detection and isolation of the protein. In certain embodiments, examples of suitable enzyme labels include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin; and examples of suitable radioactive material include iodine, carbon, sulfur, tritium, indium, technetium, thallium, gallium, palladium, molybdenum, xenon, fluorine.

[0217] In specific embodiments, antigen-binding constructs described herein are attached to macrocyclic chelators that associate with radiometal ions.

[0218] In some embodiments, the antigen-binding constructs described herein are modified by either natural processes, such as post-translational processing, or by chemical modification techniques which are well known in the art. In certain embodiments, the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. In certain embodiments, polypeptides from antigen-binding constructs described herein are branched, for example, as a result of ubiquitination, and in some embodiments are cyclic, with or without branching. Cyclic, branched, and branched cyclic polypeptides are a result from posttranslation natural processes or made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphotidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, PROTEINS—STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); POST-TRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., Meth. Enzymol. 182:626-646 (1990); Rattan et al., Ann. N.Y. Acad. Sci. 663:48-62 (1992)).

[0219] In certain embodiments, antigen-binding constructs described herein are attached to solid supports, which are particularly useful for immunoassays or purification of polypeptides that are bound by, that bind to, or associate with proteins described herein. Such solid supports include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

Pharmaceutical Compositions

[0220] Also provided herein are pharmaceutical compositions comprising an antigen-binding construct described herein. Pharmaceutical compositions comprise the construct and a pharmaceutically acceptable carrier.

[0221] The term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be

sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. In some aspects, the carrier is a man-made carrier not found in nature. Water can be used as a carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E. W. Martin. Such compositions will contain a therapeutically effective amount of the compound, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

[0222] In certain embodiments, the composition comprising the construct is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

[0223] In certain embodiments, the compositions described herein are formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with anions such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with cations such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxide isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

Methods of Treatment

[0224] In certain embodiments, provided is a method of treating a disease or disorder comprising administering to a subject in which such treatment, prevention or amelioration is desired, an antigen-binding construct described herein, in an amount effective to treat, prevent or ameliorate the disease or disorder.

[0225] "Disorder" refers to any condition that would benefit from treatment with an antigen-binding construct or method described herein. This includes chronic and acute disorders or diseases including those pathological conditions which predispose the mammal to the disorder in question. In some embodiments, the disorder is cancer, as described in more detail below.

[0226] The term "subject" refers to an animal, in some embodiments a mammal, which is the object of treatment, observation or experiment. An animal may be a human, a non-human primate, a companion animal (e.g., dogs, cats, and the like), farm animal (e.g., cows, sheep, pigs, horses, and the like) or a laboratory animal (e.g., rats, mice, guinea pigs, and the like).

[0227] The term "mammal" as used herein includes but is not limited to humans, non-human primates, canines, felines, murines, bovines, equines, and porcines.

[0228] "Treatment" refers to clinical intervention in an attempt to alter the natural course of the individual or cell being treated, and can be performed either for prophylaxis or during the course of clinical pathology. Desirable effects of treatment include preventing occurrence or recurrence of disease, alleviation of symptoms, diminishing of any direct or indirect pathological consequences of the disease, preventing metastasis, decreasing the rate of disease progression, amelioration or palliation of the disease state, and remission or improved prognosis. In some embodiments, antigen-binding constructs described herein are used to delay development of a disease or disorder. In one embodiment, antigen-binding constructs and methods described herein effect tumor regression. In one embodiment, antigen-binding constructs and methods described herein effect inhibition of tumor/cancer growth.

[0229] Desirable effects of treatment include, but are not limited to, preventing occurrence or recurrence of disease, alleviation of symptoms, diminishment of any direct or indirect pathological consequences of the disease, preventing metastasis, decreasing the rate of disease progression, amelioration or palliation of the disease state, improved survival, and remission or improved prognosis. In some embodiments, antigen-binding constructs described herein are used to delay development of a disease or to slow the progression of a disease.

[0230] The term "effective amount" as used herein refers to that amount of construct being administered, which will accomplish the goal of the recited method, e.g., relieve to some extent one or more of the symptoms of the disease, condition or disorder being treated. The amount of the composition described herein which will be effective in the treatment, inhibition and prevention of a disease or disorder associated with aberrant expression and/or activity of a therapeutic protein can be determined by standard clinical techniques. In addition, in vitro assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses are extrapolated from dose-response curves derived from in vitro or animal model test systems.

[0231] The antigen-binding construct is administered to the subject. Various delivery systems are known and can be used to administer an antigen-binding construct formulation described herein, e.g., encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the compound, receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)), construction of a nucleic acid as part of a retroviral or other vector, etc. Methods of introduction include but are not limited to intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The compounds or compositions may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. In addition, in certain embodiments, it is desirable to introduce the antigen-binding construct compositions described herein into the central nervous system by any suitable route, including intraventricular and intrathecal injection; intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir. Pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

[0232] In a specific embodiment, it is desirable to administer the antigen-binding constructs, or compositions described herein locally to the area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion during surgery, topical application, e.g., in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. Preferably, when administering a protein, including an antigen-binding construct, described herein, care must be taken to use materials to which the protein does not absorb.

[0233] In another embodiment, the antigen-binding constructs or composition can be delivered in a vesicle, in particular a liposome (see Langer, Science 249:1527-1533 (1990); Treat et al., in Liposomes in the Therapy of Infectious Disease and Cancer, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353-365 (1989); Lopez-Berestein, ibid., pp. 317-327; see generally ibid.)

[0234] In yet another embodiment, the antigen-binding constructs or composition can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, supra; Sefton, CRC Crit. Ref. Biomed. Eng. 14:201 (1987); Buchwald et al., Surgery 88:507 (1980); Saudek et al., N. Engl. J. Med. 321:574 (1989)). In another embodiment, polymeric materials can be used (see Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Pres., Boca Raton, Fla. (1974); Controlled Drug Bioavailability, Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, J., Macromol. Sci. Rev. Macromol. Chem. 23:61 (1983); see also Levy et al., Science 228:190 (1985); During et al., Ann. Neurol. 25:351 (1989); Howard et al., J. Neurosurg. 71:105 (1989)). In yet another embodiment, a controlled release system can be placed in proximity of the therapeutic target, e.g., the brain, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in Medical Applications of Controlled Release, vol. 2, pp. 115-138 (1984)).

[0235] In a specific embodiment comprising a nucleic acid encoding antigen-binding constructs decribed herein, the nucleic acid can be administered in vivo to promote expression of its encoded protein, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, e.g., by use of a retroviral vector (see U.S. Pat. No. 4,980,286), or by direct injection, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox-like peptide which is known to enter the nucleus (see e.g., Joliot et al., Proc. Natl. Acad. Sci. USA 88:1864-1868 (1991)), etc. Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination.

[0236] In certain embodiments an antigen-binding construct described herein is administered as a combination with antigen-binding constructs with non-overlapping binding target epitopes.

[0237] The amount of the antigen-binding construct which will be effective in the treatment, inhibition and prevention of a disease or disorder can be determined by standard clinical techniques. In addition, in vitro assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses are extrapolated from dose-response curves derived from in vitro or animal model test systems.

[0238] The antigen-binding constructs described herein may be administered alone or in combination with other types of treatments (e.g., radiation therapy, chemotherapy, hormonal therapy, immunotherapy and anti-tumor agents). Generally, administration of products of a species origin or species reactivity (in the case of antibodies) that is the same species as that of the patient is preferred. Thus, in an embodiment, human antigen-binding constructs, fragments derivatives, analogs, or nucleic acids, are administered to a human patient for therapy or prophylaxis.

Methods of Treating Cancers

[0239] Described herein are methods of treating a HER2+ cancer or a tumor in a subject, and methods of inhibiting the growth of a HER2+ tumor cell or killing a HER2+ tumor cell using the antigen-binding constructs described herein.

[0240] By a HER2+ cancer is meant a cancer that expresses HER2 such that the antigen-binding constructs described herein are able to bind to the cancer. As is known in the art, HER2+ cancers express HER2 at varying levels. To determine ErbB, e.g. ErbB2 (HER2) expression in the cancer, various diagnostic/prognostic assays are available. In one embodiment, ErbB2 overexpression may be analyzed by IHC, e.g. using the HERCEPTEST® (Dako). Paraffin embedded tissue sections from a tumor biopsy may be subjected to the IHC assay and accorded a ErbB2 protein staining intensity criteria as follows:

[0241] Score 0 no staining is observed or membrane staining is observed in less than 10% of tumor cells.

[0242] Score 1+ a faint/barely perceptible membrane staining is detected in more than 10% of the tumor cells. The cells are only stained in part of their membrane.

[0243] Score 2+ a weak to moderate complete membrane staining is observed in more than 10% of the tumor cells.

[0244] Score 3+ a moderate to strong complete membrane staining is observed in more than 10% of the tumor cells.

[0245] Those tumors with 0 or 1+ scores for ErbB2 overexpression assessment may be characterized as not overexpressing ErbB2, whereas those tumors with 2+ or 3+ scores may be characterized as overexpressing ErbB2.

[0246] Alternatively, or additionally, fluorescence in situ hybridization (FISH) assays such as the INFORM™ (sold by Ventana, Ariz.) or PATHVISION™ (Vysis, Ill.) may be carried out on formalin-fixed, paraffin-embedded tumor tissue to determine the extent (if any) of ErbB2 overexpression in the tumor. In comparison with IHC assay, the FISH assay, which measures HER2 gene amplification, seems to correlate better with response of patients to treatment with HERCEPTIN®, and is currently considered to be the preferred assay to identify patients likely to benefit from HERCEPTIN® treatment.

[0247] Table D describes the expression level of HER2 on several representative breast cancer and other cancer cell lines (Subik et al. (2010) Breast Cancer: Basic Clinical Research: 4; 35-41; Prang et a. (2005) British Journal of Cancer Research: 92; 342-349). As shown in the table, MCF-7 and MDA-MB-231 cells are considered to be low HER2 expressing cells; JIMT-1, and ZR-75-1 cells are considered to be medium HER2 expressing cells, and SKBR3 and BT-474 cells are considered to be high HER2 expressing cells. SKOV3 (ovarian cancer) cells are considered to be medium HER2 expressing cells.

[0248] Described herein are methods of treating a subject having a HER2+ cancer or a tumor comprising providing to the subject an effective amount of a pharmaceutical composition comprising an antigen-binding construct described herein.

[0249] Also described herein is the use of an HER2 antigen-binding construct described herein for the manufacture of a medicament for treating a cancer or a tumor. Also described herein are HER2 antigen-binding constructs for use in the treatment of cancer or a tumor.

[0250] In some embodiments, the subject being treated has pancreatic cancer, head and neck cancer, gastric cancer, colorectal cancer, breast cancer, renal cancer, cervical cancer, ovarian cancer, brain cancer, endometrial cancer, bladder cancer, non-small cell lung cancer or an epidermal-derived cancer. In some embodiments, the tumor is metastatic.

[0251] In general, the tumor in the subject being treated expresses an average of 10,000 or more copies of HER2 per tumor cell. In certain embodiments the tumor is HER2 0-1+, 1+, HER2 2+ or HER2 3+ as determined by IHC. In some embodiments the tumor is HER2 2+ or lower, or HER2 1+ or lower. In some embodiments, the tumor has an amplified HER2 gene. In some embodiments the HER2 gene is non-amplified.

[0252] In some embodiments, the tumor of the subject being treated with the antigen-binding constructs is a breast cancer. In some embodiments, the breast cancer expresses HER2 at a 3+ level. In some embodiments the breast cancer expresses HER2 at less than a 3+ level. In a specific embodiment, the breast cancer expresses HER2 at a 2+ level or lower. In a specific embodiment, the breast cancer expresses HER2 at a 1+ level or lower. In some embodiments, the breast cancer expresses estrogen receptors (ER+) and/or progesterone receptors (PR+). In some embodiments, the breast cancer is ER− and or PR−. In some embodiments the breast cancer has an amplified HER2 gene. In some embodiments the HER2 gene is non-amplified. In some embodiments, the breast cancer is a HER2 3+ estrogen receptor negative (ER−), progesterone receptor negative (PR−), trastuzumab resistant, chemotherapy resistant invasive ductal breast cancer. In another embodiment, the breast cancer is a HER2 3+ER−, PR−, trastuzumab resistant inflammatory breast cancer. In another embodiment, the breast cancer is a HER2 3+, ER−, PR−, invasive ductal carcinoma. In another embodiment, the breast cancer is a HER2 2+ HER2 gene amplified trastuzumab and pertuzumab resistant breast cancer. In some embodiments, the breast cancer is triple negative (ER−, PR− and low HER2-expressing). In some embodiments the breast cancer is resistant or refractory to trastuzumab, pertuzumab and/or trastuzumab conjugated to DM1 (ado-trastuzumab emtansine or T-DM1).

[0253] In one embodiment, the tumor is an HER2 2/3+ ovarian epithelial adenocarcinoma having an amplified HER2 gene.

[0254] Provided herein are methods for treating a subject having a HER2+ tumor that is resistant or becomes resistant to other standard-of-care therapies comprising administering to the subject a pharmaceutical composition comprising the antigen-binding constructs described herein. In certain embodiments the antigen-binding constructs described herein are provided to subjects that are unresponsive to current therapies, optionally in combination with one or more current anti-HER2 therapies. In some embodiments the current anti-HER2 therapies include, but are not limited to, anti-HER2 or anti-HER3 monospecific bivalent antibodies, trastuzumab, pertuzumab, T-DM1, a bi-specific HER2/HER3 scFv, or combinations thereof. In some embodiments, the cancer is resistant to various chemotherapeutic agents such as taxanes. In some embodiments the cancer is resistant to trastuzumab. In some embodiment the cancer is resistant to pertuzumab. In one embodiment, the cancer is resistant or refractory to TDM1 (trastuzumab conjugated to DM1). In some embodiments, the subject has previously been treated with an anti-HER2 antibody such as trastuzumab, pertuzumab or DM1. In some embodiments, the subject has not been previously treated with an anti-HER2 antibody. In one embodiment, the antigen-binding construct is provided to a subject for the treatment of metastatic cancer when the patient has progressed on previous anti-HER2 therapy.

[0255] Provided herein are methods of treating a subject having a HER2+ tumor comprising providing an effective amount of a pharmaceutical composition comprising an antigen-binding construct described herein in conjunction with an additional anti-tumor agent. The additional anti-tumor agent may be a therapeutic antibody as noted above, or a chemotherapeutic agent. Chemotherapeutic agents useful for use in combination with the antigen-binding constructs of the invention include cisplatin, carboplatin, paclitaxel, albumin-bound paclitaxel, nab-paclitaxel, docetaxel, gemcitabine, vinorelbine, irinotecan, etoposide, vinblastine, pemetrexed, 5-fluorouracil (with or without folinic acid), capecitabine, carboplatin, epirubicin, oxaliplatin, folfirinox,

abraxane, navelbine and cyclophosphamide, capecitabine, gemcitabine, navelbine, paclitaxel, nab-paclitaxel.

[0256] In some embodiments, the tumor is non-small cell lung cancer, and the additional agent is one or more of cisplatin, carboplatin, paclitaxel, albumin-bound paclitaxel, nab-paclitaxel, capecitabine, navelbine, docetaxel, gemcitabine, vinorelbine, irinotecan, etoposide, vinblastine or pemetrexed. In embodiments, the tumor is gastric or stomach cancer, and the additional agent is one or more of 5-fluorouracil (with or without folinic acid), capecitabine, carboplatin, cisplatin, docetaxel, epirubicin, irinotecan, oxaliplatin, nab-paclitaxel or paclitaxel. In other embodiments the tumor is pancreatic cancer, and the additional agent is one or more of nab-paclitaxel, capecitabine, navelbine, gemcitabine, folfirinox, abraxane, or 5-fluorouracil. In other embodiments the tumor is a estrogen and/or progesterone positive breast cancer, and the additional agent is one or more of paclitaxel, capecitabine, navelbine, gemcitabine, paclitaxel or nab-paclitaxel or a combination of (a) doxorubicin and epirubicin, (b) a combination of paclitaxel and docetaxel, or (c) a combination of 5-fluorouracil, cyclophosphamide and carboplatin. In other embodiments, the tumor is head and neck cancer, and the additional agent is one or more of paclitaxel, capecitabine, navelbine, gemcitabine or nab-paclitaxel carboplatin, doxorubicin or cisplatin. In other embodiments, the tumor is ovarian cancer and the additional agent may be one or more of capecitabine, navelbine, gemcitabine, nab-paclitaxel, cisplatin, carboplatin, or a taxane such as paclitaxel or docetaxel.

[0257] The additional agents may be administered to the subject being treated concurrently with the antigen-binding constructs or sequentially.

[0258] The subject being treated with the antigen-binding constructs may be a human, a non-human primate or other mammal such as a mouse.

[0259] In some embodiments, the result of providing an effective amount of the antigen-binding construct to a subject having a tumor is shrinking the tumor, inhibiting growth of the tumor, increasing time to progression of the tumor, prolonging disease-free survival of the subject, decreasing metastases, increasing the progression-free survival of the subject, or increasing overall survival of the subject or increasing the overall survival of a group of subjects receiving the treatment.

[0260] Also described herein are methods of killing or inhibiting the growth of a HER2-expressing tumor cell comprising contacting the cell with the antigen-binding construct provided herein.

[0261] In various embodiments, a tumor cell may be a HER2 1+ or 2+ human pancreatic carcinoma cell, a HER2 3+ human lung carcinoma cell, a HER2 2+ human Caucasian bronchioaveolar carcinoma cell, a human pharyngeal carcinoma cell, a HER2 2+ human tongue squamous cell carcinoma cell, a HER2 2+ squamous cell carcinoma cell of the pharynx, a HER2 1+ or 2+ human colorectal carcinoma cell, a HER2 3+ human gastric carcinoma cell, a HER2 1+ human breast ductal ER+ (estrogen receptor-positive) carcinoma cell, a HER2 2+/3+ human ER+, HER2-amplified breast carcinoma cell, a HER2 0+/1+ human triple negative breast carcinoma cell, a HER2 2+ human endometrioid carcinoma cell, a HER2 1+ lung-metastatic malignant melanoma cell, a HER2 1+ human cervix carcinoma cell, Her2 1+ human renal cell carcinoma cell, or a HER2 1+ human ovary carcinoma cell.

[0262] In embodiments in which the antigen-binding constructs are conjugated to DM1, the tumor cell may be a HER2 1+ or 2+ or 3+ human pancreatic carcinoma cell, a HER2 2+ metastatic pancreatic carcinoma cell, a HER2 0+/1+, +3+ human lung carcinoma cell, a HER2 2+ human Caucasian bronchioaveolar carcinoma cell, a HER2 0+ anaplastic lung carcinoma, a human non-small cell lung carcinoma cell, a human pharyngeal carcinoma cell, a HER2 2+ human tongue squamous cell carcinoma cell, a HER2 2+ squamous cell carcinoma cell of the pharynx, a HER2 1+ or 2+ human colorectal carcinoma cell, a HER2 0+, 1+ or 3+ human gastric carcinoma cell, a HER2 1+ human breast ductal ER+ (estrogen receptor-positive) carcinoma cell, a HER2 2+/3+ human ER+, HER2-amplified breast carcinoma cell, a HER2 0+/1+ human triple negative breast carcinoma cell, a HER2 0+ human breast ductal carcinoma (Basal B, Mesenchymal-like triple negative) cell, a HER2 2+ER+ breast carcinoma, a HER2 0+ human metastatic breast carcinoma cell (ER−, HER2-amplified, luminal A, TN), a human uterus mesodermal tumor (mixed grade III) cell, a 2+ human endometrioid carcinoma cell, a HER2 1+ human skin epidermoid carcinoma cell, a HER2 1+ lung-metastatic malignant melanoma cell, a HER2 1+ malignant melanoma cell, a human cervix epidermoid carcinoma vcell, a HER2 1+ human urinary bladder carcinoma cell, a HER2 1+ human cervix carcinoma cell, Her2 1+ human renal cell carcinoma cell, or a HER2 1+, 2+ or 3+ human ovary carcinoma cell.

[0263] In some embodiments the tumor cell may be one or more of the following cell lines: pancreatic tumor cell lines BxPC3, Capan-1, MiaPaca2; lung tumor cell lines Calu-3, NCI-H322; head and neck tumor cells lines Detroit 562, SCC-25, FaDu; colorectal tumor cell lines HT29, SNU-C2B; gastric tumor cell line NCI-N87; breast tumor cell lines MCF-7, MDA-MB-175, MDA-MB-361, MDA-MB-231, BT-20, JIMT-1, SkBr3, BT-474; uterine tumor cell line TOV-112D; skin tumor cell line Malme-3M; cervical tumor cell lines Caski, MS751; bladder tumor cell line T24, ovarian tumor cell lines CaOV3, and SKOV3.

[0264] In some embodiments in which the antigen-binding constructs are conjugated to DM1, the tumor cell may be one or more of the following cell lines: pancreatic tumor cell lines BxPC3, Capan-1, MiaPaca2, SW 1990, Pancl; lung tumor cell lines A549, Calu-3, Calu-6, NCI-H2126, NCI-H322; head and neck tumor cells lines Detroit 562, SCC-15, SCC-25, FaDu; colorectal tumor cell lines Colo201, DLD-1, HCT116, HT29, SNU-C2B; gastric tumor cell lines SNU-1, SNU-16, NCI-N87; breast tumor cell lines SkBr3, MCF-7, MDA-MB-175, MDA-MB-361, MDA-MB-231, ZR-75-1, BT-20, BT549, BT-474, CAMA-1, MDA-MB-453, JIMT-1, T47D; Uterine tumor cell lines SK-UT-1, TOV-112D; skin tumor cell lines A431, Malme-3M, SKEMEL28; cervical tumor cell lines Caski, MS751; bladder tumor cell line T24, renal tumor cell line ACHN; ovarian tumor cell lines CaOV3, Ovar-3, and SKOV3.

[0265] Also described herein are methods of treating a subject having a HER2 expressing (HER2+) tumor such as a HER2+ lung, head and neck, or breast tumor by administering an antigen binding construct disclosed herein. In some aspects, the tumor volume in the subject after receiving at least seven doses of the antigen binding construct is less than the tumor volume of a control subject receiving an equivalent amount of trastuzumab. In some aspects, the survival of the subject receiving the antigen binding con-

struct is increased as compared to a control subject receiving an equivalent amount of a non-specific control antibody or as compared to a control subject not receiving treatment.

[0266] In some aspects, the tumor is a lung tumor, optionally wherein the tumor is a non-squamous non-small cell lung tumor that is HER2-low, non-HER2 gene amplified. In some aspects, the tumor is HER3+. In some aspects, the tumor is EGFR low. In some aspects, the tumor is moderately sensitive to Cisplatin at the MTD.

[0267] In some aspects, the tumor is a head and neck tumor, optionally wherein the tumor is a squamous cell tumor of the head and neck that is HER2 low, non-HER2 gene amplified. In some aspects, the tumor is HER3+ low. In some aspects, the tumor is EGFR+. In some aspects, the tumor is highly sensitive to Cisplatin at the MTD.

[0268] In some aspects, the tumor is a breast tumor, optionally wherein the tumor is a ER+/PR− breast cancer with a luminal B molecular classification.

[0269] In some aspects, the subject is administered at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 doses. In some aspects, the amount of at least one of the plurality of doses is at least 0.3, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 mg/kg. In some aspects, the amount of each of the plurality of doses is at least 0.3, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 mg/kg. In some aspects, each dose is administered at least daily, weekly, or monthly. In some aspects, each dose is administered at least every 1, 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, or 31 days. In some aspects, treatment continues for at least 1, 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, or 31 days; at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 weeks; or at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 months.

[0270] In some aspects, the mean tumor volume in the subject after receiving at least 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 doses is less than the mean tumor volume of a control subject receiving an equivalent amount of trastuzumab.

[0271] In some aspects, overall survival of the subject is significantly increased as compared to a control subject receiving an equivalent amount of a non-specific control antibody or as compared to a control subject not receiving treatment. In some aspects, the significance is measured by a log rank test. In some aspects, the p value is less than 0.5, 0.01, or 0.001.

[0272] In some aspects, overall survival of the subject is more significantly increased as compared to a control subject receiving an equivalent amount of trastuzumab. In some aspects, the antigen-binding construct p value is less than 0.001 and wherein the trastuzumab p value is greater than 0.001.

[0273] In some aspects, the p value of the significance of the increase relative to the control subject receiving an equivalent amount of a non-specific control antibody is less than the p value of an increase in survival of a second control receiving an equivalent amount of trastuzumab as compared to the control subject receiving an equivalent amount of a non-specific control antibody. In some aspects, the antigen-binding construct p value is less than 0.001 and wherein the trastuzumab p value is greater than 0.001.

[0274] In some aspects, overall survival of the subject after receiving a combination of the antigen-binding construct and an additional agent is significantly increased as compared to a control subject receiving an equivalent amount of trastuzumab alone.

[0275] In some aspects, overall survival of the subject is significantly increased as compared to a control subject receiving a lesser amount of trastuzumab.

Kits and Articles of Manufacture

[0276] Also described herein are kits comprising one or more antigen-binding construct described herein. Individual components of the kit would be packaged in separate containers and, associated with such containers, can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale. The kit may optionally contain instructions or directions outlining the method of use or administration regimen for the antigen-binding construct.

[0277] When one or more components of the kit are provided as solutions, for example an aqueous solution, or a sterile aqueous solution, the container means may itself be an inhalant, syringe, pipette, eye dropper, or other such like apparatus, from which the solution may be administered to a subject or applied to and mixed with the other components of the kit.

[0278] The components of the kit may also be provided in dried or lyophilized form and the kit can additionally contain a suitable solvent for reconstitution of the lyophilized components. Irrespective of the number or type of containers, the kits described herein also may comprise an instrument for assisting with the administration of the composition to a patient. Such an instrument may be an inhalant, nasal spray device, syringe, pipette, forceps, measured spoon, eye dropper or similar medically approved delivery vehicle.

[0279] In another aspect described herein, an article of manufacture containing materials useful for the treatment, prevention and/or diagnosis of the disorders described above is provided. The article of manufacture comprises a container and a label or package insert on or associated with the container. Suitable containers include, for example, bottles, vials, syringes, IV solution bags, etc. The containers may be formed from a variety of materials such as glass or plastic. The container holds a composition which is by itself or combined with another composition effective for treating, preventing and/or diagnosing the condition and may have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). At least one active agent in the composition is a T cell activating antigen-binding construct described herein. The label or package insert indicates that the composition is used for treating the condition of choice. Moreover, the article of manufacture may comprise (a) a first container with a composition contained therein, wherein the composition comprises an antigen-binding construct described herein; and (b) a second container with a composition contained therein, wherein the composition comprises a further cytotoxic or otherwise therapeutic agent. The article of manufacture in this embodiment described herein may further comprise a package insert indicating that the compositions can be used to treat a particular condition. Alternatively, or additionally, the article of manufacture may further comprise a second (or third)

container comprising a pharmaceutically-acceptable buffer, such as bacteriostatic water for injection (BWFI), 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, and syringes.

Polypeptides and Polynucleotides

[0280] The antigen-binding constructs described herein comprise at least one polypeptide. Also described are polynucleotides encoding the polypeptides described herein. The antigen-binding constructs are typically isolated.

[0281] As used herein, "isolated" means an agent (e.g., a polypeptide or polynucleotide) that has been identified and separated and/or recovered from a component of its natural cell culture environment. Contaminant components of its natural environment are materials that would interfere with diagnostic or therapeutic uses for the antigen-binding construct, and may include enzymes, hormones, and other proteinaceous or non-proteinaceous solutes. Isolated also refers to an agent that has been synthetically produced, e.g., via human intervention.

[0282] The terms "polypeptide," "peptide" and "protein" are used interchangeably herein to refer to a polymer of amino acid residues. That is, a description directed to a polypeptide applies equally to a description of a peptide and a description of a protein, and vice versa. The terms apply to naturally occurring amino acid polymers as well as amino acid polymers in which one or more amino acid residues is a non-naturally encoded amino acid. As used herein, the terms encompass amino acid chains of any length, including full length proteins, wherein the amino acid residues are linked by covalent peptide bonds.

[0283] The term "amino acid" refers to naturally occurring and non-naturally occurring amino acids, as well as amino acid analogs and amino acid mimetics that function in a manner similar to the naturally occurring amino acids. Naturally encoded amino acids are the 20 common amino acids (alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, praline, serine, threonine, tryptophan, tyrosine, and valine) and pyrrolysine and selenocysteine. Amino acid analogs refers to compounds that have the same basic chemical structure as a naturally occurring amino acid, i.e., an a carbon that is bound to a hydrogen, a carboxyl group, an amino group, and an R group, such as, homoserine, norleucine, methionine sulfoxide, methionine methyl sulfonium. Such analogs have modified R groups (such as, norleucine) or modified peptide backbones, but retain the same basic chemical structure as a naturally occurring amino acid. Reference to an amino acid includes, for example, naturally occurring proteogenic L-amino acids; D-amino acids, chemically modified amino acids such as amino acid variants and derivatives; naturally occurring non-proteogenic amino acids such as β-alanine, ornithine, etc.; and chemically synthesized compounds having properties known in the art to be characteristic of amino acids. Examples of non-naturally occurring amino acids include, but are not limited to, a-methyl amino acids (e.g. a-methyl alanine), D-amino acids, histidine-like amino acids (e.g., 2-amino-histidine, β-hydroxy-histidine, homohistidine), amino acids having an extra methylene in the side chain ("homo" amino acids), and amino acids in which a carboxylic acid functional group in the side chain is replaced with a sulfonic acid group (e.g., cysteic acid). The incorporation of non-natural amino acids, including synthetic non-native amino acids, substituted amino acids, or one or more D-amino acids into the proteins of the present invention may be advantageous in a number of different ways. D-amino acid-containing peptides, etc., exhibit increased stability in vitro or in vivo compared to L-amino acid-containing counterparts. Thus, the construction of peptides, etc., incorporating D-amino acids can be particularly useful when greater intracellular stability is desired or required. More specifically, D-peptides, etc., are resistant to endogenous peptidases and proteases, thereby providing improved bioavailability of the molecule, and prolonged lifetimes in vivo when such properties are desirable. Additionally, D-peptides, etc., cannot be processed efficiently for major histocompatibility complex class II-restricted presentation to T helper cells, and are therefore, less likely to induce humoral immune responses in the whole organism.

[0284] Amino acids may be referred to herein by either their commonly known three letter symbols or by the one-letter symbols recommended by the IUPAC-IUB Biochemical Nomenclature Commission. Nucleotides, likewise, may be referred to by their commonly accepted single-letter codes.

[0285] Also included in the invention are polynucleotides encoding polypeptides of the antigen-binding constructs. The term "polynucleotide" or "nucleotide sequence" is intended to indicate a consecutive stretch of two or more nucleotide molecules. The nucleotide sequence may be of genomic, cDNA, RNA, semisynthetic or synthetic origin, or any combination thereof.

[0286] The term "nucleic acid" refers to deoxyribonucleotides, deoxyribonucleosides, ribonucleosides, or ribonucleotides and polymers thereof in either single- or double-stranded form. Unless specifically limited, the term encompasses nucleic acids containing known analogues of natural nucleotides which have similar binding properties as the reference nucleic acid and are metabolized in a manner similar to naturally occurring nucleotides. Unless specifically limited otherwise, the term also refers to oligonucleotide analogs including PNA (peptidonucleic acid), analogs of DNA used in antisense technology (phosphorothioates, phosphoroamidates, and the like). Unless otherwise indicated, a particular nucleic acid sequence also implicitly encompasses conservatively modified variants thereof (including but not limited to, degenerate codon substitutions) and complementary sequences as well as the sequence explicitly indicated. Specifically, degenerate codon substitutions may be achieved by generating sequences in which the third position of one or more selected (or all) codons is substituted with mixed-base and/or deoxyinosine residues (Batzer et al., Nucleic Acid Res. 19:5081 (1991); Ohtsuka et al., J. Biol. Chem. 260:2605-2608 (1985); Rossolini et al., Mol. Cell. Probes 8:91-98 (1994)).

[0287] "Conservatively modified variants" applies to both amino acid and nucleic acid sequences. With respect to particular nucleic acid sequences, "conservatively modified variants" refers to those nucleic acids which encode identical or essentially identical amino acid sequences, or where the nucleic acid does not encode an amino acid sequence, to essentially identical sequences. Because of the degeneracy of the genetic code, a large number of functionally identical nucleic acids encode any given protein. For instance, the codons GCA, GCC, GCG and GCU all encode the amino

acid alanine. Thus, at every position where an alanine is specified by a codon, the codon can be altered to any of the corresponding codons described without altering the encoded polypeptide. Such nucleic acid variations are "silent variations," which are one species of conservatively modified variations. Every nucleic acid sequence herein which encodes a polypeptide also describes every possible silent variation of the nucleic acid. One of ordinary skill in the art will recognize that each codon in a nucleic acid (except AUG, which is ordinarily the only codon for methionine, and TGG, which is ordinarily the only codon for tryptophan) can be modified to yield a functionally identical molecule. Accordingly, each silent variation of a nucleic acid which encodes a polypeptide is implicit in each described sequence.

[0288] As to amino acid sequences, one of ordinary skill in the art will recognize that individual substitutions, deletions or additions to a nucleic acid, peptide, polypeptide, or protein sequence which alters, adds or deletes a single amino acid or a small percentage of amino acids in the encoded sequence is a "conservatively modified variant" where the alteration results in the deletion of an amino acid, addition of an amino acid, or substitution of an amino acid with a chemically similar amino acid. Conservative substitution tables providing functionally similar amino acids are known to those of ordinary skill in the art. Such conservatively modified variants are in addition to and do not exclude polymorphic variants, interspecies homologs, and alleles described herein.

[0289] Conservative substitution tables providing functionally similar amino acids are known to those of ordinary skill in the art. The following eight groups each contain amino acids that are conservative substitutions for one another: 1) Alanine (A), Glycine (G); 2) Aspartic acid (D), Glutamic acid (E); 3) Asparagine (N), Glutamine (Q); 4) Arginine (R), Lysine (K); 5) Isoleucine (I), Leucine (L), Methionine (M), Valine (V); 6) Phenylalanine (F), Tyrosine (Y), Tryptophan (W); 7) Serine (S), Threonine (T); and [0139] 8) Cysteine (C), Methionine (M) (see, e.g., Creighton, Proteins: Structures and Molecular Properties (W H Freeman & Co.; 2nd edition (December 1993)

[0290] The terms "identical" or percent "identity," in the context of two or more nucleic acids or polypeptide sequences, refer to two or more sequences or subsequences that are the same. Sequences are "substantially identical" if they have a percentage of amino acid residues or nucleotides that are the same (i.e., about 60% identity, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, or about 95% identity over a specified region), when compared and aligned for maximum correspondence over a comparison window, or designated region as measured using one of the following sequence comparison algorithms (or other algorithms available to persons of ordinary skill in the art) or by manual alignment and visual inspection. This definition also refers to the complement of a test sequence. The identity can exist over a region that is at least about 50 amino acids or nucleotides in length, or over a region that is 75-100 amino acids or nucleotides in length, or, where not specified, across the entire sequence of a polynucleotide or polypeptide. A polynucleotide encoding a polypeptide of the present invention, including homologs from species other than human, may be obtained by a process comprising the steps of screening a library under stringent hybridization conditions with a labeled probe having a polynucleotide sequence described herein or a fragment thereof, and isolating full-length cDNA and genomic clones containing said polynucleotide sequence. Such hybridization techniques are well known to the skilled artisan.

[0291] For sequence comparison, typically one sequence acts as a reference sequence, to which test sequences are compared. When using a sequence comparison algorithm, test and reference sequences are entered into a computer, subsequence coordinates are designated, if necessary, and sequence algorithm program parameters are designated. Default program parameters can be used, or alternative parameters can be designated. The sequence comparison algorithm then calculates the percent sequence identities for the test sequences relative to the reference sequence, based on the program parameters.

[0292] A "comparison window", as used herein, includes reference to a segment of any one of the number of contiguous positions selected from the group consisting of from 20 to 600, usually about 50 to about 200, more usually about 100 to about 150 in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned. Methods of alignment of sequences for comparison are known to those of ordinary skill in the art. Optimal alignment of sequences for comparison can be conducted, including but not limited to, by the local homology algorithm of Smith and Waterman (1970) Adv. Appl. Math. 2:482c, by the homology alignment algorithm of Needleman and Wunsch (1970) J. Mol. Biol. 48:443, by the search for similarity method of Pearson and Lipman (1988) Proc. Nat'l. Acad. Sci. USA 85:2444, by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, Wis.), or by manual alignment and visual inspection (see, e.g., Ausubel et al., Current Protocols in Molecular Biology (1995 supplement)).

[0293] One example of an algorithm that is suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul et al. (1997) Nuc. Acids Res. 25:3389-3402, and Altschul et al. (1990) J. Mol. Biol. 215:403-410, respectively. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information available at the World Wide Web at ncbi.nlm.nih.gov. The BLAST algorithm parameters W, T, and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, an expectation (E) or 10, M=5, N=−4 and a comparison of both strands. For amino acid sequences, the BLASTP program uses as defaults a wordlength of 3, and expectation (E) of 10, and the BLOSUM62 scoring matrix (see Henikoff and Henikoff (1992) Proc. Natl. Acad. Sci. USA 89:10915) alignments (B) of 50, expectation (E) of 10, M=5, N=−4, and a comparison of both strands. The BLAST algorithm is typically performed with the "low complexity" filter turned off

[0294] The BLAST algorithm also performs a statistical analysis of the similarity between two sequences (see, e.g., Karlin and Altschul (1993) Proc. Natl. Acad. Sci. USA 90:5873-5787). One measure of similarity provided by the BLAST algorithm is the smallest sum probability (P(N)), which provides an indication of the probability by which a match between two nucleotide or amino acid sequences would occur by chance. For example, a nucleic acid is

considered similar to a reference sequence if the smallest sum probability in a comparison of the test nucleic acid to the reference nucleic acid is less than about 0.2, or less than about 0.01, or less than about 0.001.

[0295] The phrase "selectively (or specifically) hybridizes to" refers to the binding, duplexing, or hybridizing of a molecule only to a particular nucleotide sequence under stringent hybridization conditions when that sequence is present in a complex mixture (including but not limited to, total cellular or library DNA or RNA).

[0296] The phrase "stringent hybridization conditions" refers to hybridization of sequences of DNA, RNA, or other nucleic acids, or combinations thereof under conditions of low ionic strength and high temperature as is known in the art. Typically, under stringent conditions a probe will hybridize to its target subsequence in a complex mixture of nucleic acid (including but not limited to, total cellular or library DNA or RNA) but does not hybridize to other sequences in the complex mixture. Stringent conditions are sequence-dependent and will be different in different circumstances. Longer sequences hybridize specifically at higher temperatures. An extensive guide to the hybridization of nucleic acids is found in Tijssen, Laboratory Techniques in Biochemistry and Molecular Biology—Hybridization with Nucleic Probes, "Overview of principles of hybridization and the strategy of nucleic acid assays" (1993).

[0297] As used herein, the terms "engineer, engineered, engineering", are considered to include any manipulation of the peptide backbone or the post-translational modifications of a naturally occurring or recombinant polypeptide or fragment thereof. Engineering includes modifications of the amino acid sequence, of the glycosylation pattern, or of the side chain group of individual amino acids, as well as combinations of these approaches. The engineered proteins are expressed and produced by standard molecular biology techniques.

[0298] By "isolated nucleic acid molecule or polynucleotide" is intended a nucleic acid molecule, DNA or RNA, which has been removed from its native environment. For example, a recombinant polynucleotide encoding a polypeptide contained in a vector is considered isolated. Further examples of an isolated polynucleotide include recombinant polynucleotides maintained in heterologous host cells or purified (partially or substantially) polynucleotides in solution. An isolated polynucleotide includes a polynucleotide molecule contained in cells that ordinarily contain the polynucleotide molecule, but the polynucleotide molecule is present extrachromosomally or at a chromosomal location that is different from its natural chromosomal location. Isolated RNA molecules include in vivo or in vitro RNA transcripts, as well as positive and negative strand forms, and double-stranded forms. Isolated polynucleotides or nucleic acids described herein, further include such molecules produced synthetically, e.g., via PCR or chemical synthesis. In addition, a polynucleotide or a nucleic acid, in certain embodiments, include a regulatory element such as a promoter, ribosome binding site, or a transcription terminator.

[0299] The term "polymerase chain reaction" or "PCR" generally refers to a method for amplification of a desired nucleotide sequence in vitro, as described, for example, in U.S. Pat. No. 4,683,195. In general, the PCR method involves repeated cycles of primer extension synthesis, using oligonucleotide primers capable of hybridising preferentially to a template nucleic acid.

[0300] By a nucleic acid or polynucleotide having a nucleotide sequence at least, for example, 95% "identical" to a reference nucleotide sequence of the present invention, it is intended that the nucleotide sequence of the polynucleotide is identical to the reference sequence except that the polynucleotide sequence may include up to five point mutations per each 100 nucleotides of the reference nucleotide sequence. In other words, to obtain a polynucleotide having a nucleotide sequence at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence may be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence may be inserted into the reference sequence. These alterations of the reference sequence may occur at the 5' or 3' terminal positions of the reference nucleotide sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence. As a practical matter, whether any particular polynucleotide sequence is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a nucleotide sequence of the present invention can be determined conventionally using known computer programs, such as the ones discussed above for polypeptides (e.g. ALIGN-2).

[0301] A derivative, or a variant of a polypeptide is said to share "homology" or be "homologous" with the peptide if the amino acid sequences of the derivative or variant has at least 50% identity with a 100 amino acid sequence from the original peptide. In certain embodiments, the derivative or variant is at least 75% the same as that of either the peptide or a fragment of the peptide having the same number of amino acid residues as the derivative. In certain embodiments, the derivative or variant is at least 85% the same as that of either the peptide or a fragment of the peptide having the same number of amino acid residues as the derivative. In certain embodiments, the amino acid sequence of the derivative is at least 90% the same as the peptide or a fragment of the peptide having the same number of amino acid residues as the derivative. In some embodiments, the amino acid sequence of the derivative is at least 95% the same as the peptide or a fragment of the peptide having the same number of amino acid residues as the derivative. In certain embodiments, the derivative or variant is at least 99% the same as that of either the peptide or a fragment of the peptide having the same number of amino acid residues as the derivative.

[0302] The term "modified," as used herein refers to any changes made to a given polypeptide, such as changes to the length of the polypeptide, the amino acid sequence, chemical structure, co-translational modification, or post-translational modification of a polypeptide. The form "(modified)" term means that the polypeptides being discussed are optionally modified, that is, the polypeptides under discussion can be modified or unmodified.

[0303] In some aspects, an antigen-binding construct comprises an amino acid sequence that is at least 80, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100% identical to a relevant amino acid sequence or fragment thereof set forth in the Table(s) or accession number(s) disclosed herein. In some aspects, an isolated antigen-binding construct comprises an amino acid sequence encoded by a polynucleotide that is at least 80, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100%

identical to a relevant nucleotide sequence or fragment thereof set forth in Table(s) or accession number(s) disclosed herein.

[0304] It is to be understood that this invention is not limited to the particular protocols; cell lines, constructs, and reagents described herein and as such may 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 limit the scope of the present invention

[0305] All publications and patents mentioned herein are incorporated herein by reference for the purpose of describing and disclosing, for example, the constructs and methodologies that are described in the publications, which might be used in connection with the presently described invention. The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the inventors are not entitled to antedate such disclosure by virtue of prior invention or for any other reason.

EXAMPLES

[0306] Below are examples of specific embodiments for carrying out the present invention. The examples are offered for illustrative purposes only, and are not intended to limit the scope of the present invention in any way. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperatures, etc.), but some experimental error and deviation should, of course, be allowed for.

[0307] The practice of the present invention will employ, unless otherwise indicated, conventional methods of protein chemistry, biochemistry, recombinant DNA techniques and pharmacology, within the skill of the art. Such techniques are explained fully in the literature. See, e.g., T. E. Creighton, *Proteins: Structures and Molecular Properties* (W.H. Freeman and Company, 1993); A. L. Lehninger, *Biochemistry* (Worth Publishers, Inc., current addition); Sambrook, et al., *Molecular Cloning: A Laboratory Manual* (2nd Edition, 1989); *Methods In Enzymology* (S. Colowick and N. Kaplan eds., Academic Press, Inc.); *Remington's Pharmaceutical Sciences,* 18th Edition (Easton, Pa.: Mack Publishing Company, 1990); Carey and Sundberg *Advanced Organic Chemistry* 3rd Ed. (Plenum Press) Vols A and B (1992).

Example 1: Preparation of Exemplary Anti-HER2 Bispecific Antibodies and Controls

[0308] A number of exemplary anti-HER2 biparatopic antibodies (or antigen-binding constructs) and controls were prepared as described below. The antibodies and controls have been prepared in different formats, and representations of exemplary biparatopic formats are shown in FIG. **1**. In all of the formats shown in FIG. **1**, the heterodimeric Fc is depicted with one chain (Chain A) shown in black and the other (Chain B) shown in grey, while one antigen-binding domain (1) is shown in hatched fill, while the other antigen-binding domain (2) is shown in white.

[0309] FIG. **1**A depicts the structure of a biparatopic antibody in a Fab-Fab format. FIGS. **1**B to **1**E depict the structure of possible versions of a biparatopic antibody in an scFv-Fab format. In FIG. **1**B, antigen-binding domain 1 is an scFv, fused to Chain A, while antigen-binding domain 2 is a Fab, fused to Chain B. In FIG. **1**C, antigen-binding domain 1 is a Fab, fused to Chain A, while antigen-binding domain 2 is an scFv, fused to Chain B. In FIG. **1**D, antigen-binding domain 2 is a Fab, fused to Chain A, while antigen-binding domain 1 is an scFv, fused to Chain B. In FIG. **1**E, antigen-binding domain 2 is an scFv, fused to Chain A, while antigen-binding domain 1 is a Fab, fused to Chain B. In FIG. **1**F, both antigen-binding domains are scFvs.

[0310] The sequences of the following variants are provided in the Sequence Table found after the Examples. CDR regions were identified using a combination of the Kabat and Chothia methods. Regions may vary slightly based on method used for identification.

[0311] Exemplary Anti-HER2 Biparatopic Antibodies

[0312] Exemplary anti-HER2 biparatopic antibodies were prepared as shown in Table 1.

TABLE 1

Exemplary anti-HER2 biparatbopic antibodies

Variant		Chain A	Chain B
5019	domain containing the epitope	ECD2	ECD4
	Format	Fab	scFv
	Antibody name	Pertuzumab	Trastuzumab
	CH3 sequence substitutions	T350V_L351Y_F405A_Y407V	T366I_N390R_K392M_T394W
5020	domain containing the epitope	ECD4	ECD2
	format	scFv	Fab
	Antibody name	Trastuzumab	Pertuzumab
	CH3 sequence substitutions	L351Y_S400E_F405A_Y407V	T350V_T366L_K392L_T394W
7091	domain containing the epitope	ECD2	ECD4

TABLE 1-continued

Exemplary anti-HER2 biparatbopic antibodies

Variant		Chain A	Chain B
	format	Fab	scFv
	Antibody name	Pertuzumab	Trastuzumab
	CH3 sequence substitutions	T350V_L351Y_F405A_Y407V	T350V_T366L_K392L_T394W
10000	domain containing the epitope	ECD2	ECD4
	format	Fab	scFv
	Antibody name	Pertuzumab - with Y96A in VL region and T30A/A49G/L69F in VH region	Trastuzumab
	CH3 sequence substitutions	T350V_L351Y_F405A_Y407V	T350V_T366L_K392L_T394W
6902	domain containing the epitope	ECD2	ECD4
	format	Fab	Fab
	Antibody name	Trastuzumab	Pertuzumab
	Fab substitutions	HC: L143E_K145T LC: Q124R	HC: D146G_Q179K LC: Q124E_Q160E_T180E
	CH3 sequence substitutions	T350V_L351Y_F405A_Y407V	T350V_T366L_K392L_T394W
6903	domain containing the epitope	ECD2	ECD4
	format	Fab	Fab
	Fab substitutions	HC: L143E_K145T LC: Q124R_Q1160K_T178R	HC: D146G_Q179K LC: Q124E_Q160E_T180E
	Antibody name	Trastuzumab	Pertuzumab
	CH3 sequence substitutions	T350V_L351Y_F405A_Y407V	T350V_T366L_K392L_T394W
6717	domain containing the epitope	ECD4	ECD2
	format	scFv	scFv
	Antibody name	Pertuzumab	Trastuzumab
	CH3 sequence substitutions	T350V_L351Y_F405A_Y407V	T366I_N390R_K392M_T394W

Notes:

CH3 numbering according to EU index as in Kabat referring to the numbering of the EU antibody (Edelman et al., 1969, Proc Natl Acad Sci USA 63: 78-85);

Fab or variable domain numbering according to Kabat (Kabat and Wu, 1991; Kabat et al, Sequences of proteins of immunological interest. 5th Edition - US Department of Health and Human Services, NIH publication no 91-3242, p 647 (1991))

"domain containing the epitope" = domain of HER2 to which antigen-binding moiety binds;

"Antibody name" = antibody from which antigen-binding moiety is derived, includes substitutions compared to wild-type when present;

"Fab substitutions" = substitutions in Fab that promote correct light chain pairing;

"CH3 sequence substitutions" = substitutions in CH3 domain that promote formation of heterodimeric Fc

[0313] Exemplary Anti-HER2 Monovalent Control Antibodies

[0314] v1040: a monovalent anti-HER2 antibody, where the HER2 binding domain is a Fab derived from trastuzumab on chain A, and the Fc region is a heterodimer having the mutations T350V_L351Y_F405A_Y407V in Chain A, T350V_T366L_K392L_T394W in Chain B, and the hinge region of Chain B having the mutation C226S; the antigen-binding domain binds to domain 4 of HER2.

[0315] v630—a monovalent anti-HER2 antibody, where the HER2 binding domain is an scFv derived from trastuzumab on Chain A, and the Fc region is a heterodimer having the mutations L351Y_S400E_F405A_Y407V in Chain A, T366I_N390R_K392M_T394W in Chain B; and the hinge region having the mutation C226S (EU numbering) in both chains; the antigen-binding domain binds to domain 4 of HER2.

[0316] v4182: a monovalent anti-HER2 antibody, where the HER2 binding domain is a Fab derived from pertuzumab on chain A, and the Fc region is a heterodimer having the mutations T350V_L351Y_F405A_Y407V in Chain A, T350V_T366L_K392L_T394W in Chain B, and the hinge region of Chain B having the mutation C226S; the antigen-binding domain binds to domain 2 of HER2.

[0317] Exemplary Anti-HER2 Monospecific Bivalent Antibody Controls (Full-Sized Antibodies, FSAs)

[0318] v506 is a wild-type anti HER2 produced in-house in Chinese Hamster Ovary (CHO) cells, as a control. Both HER2 binding domains are derived from trastuzumab in the Fab format and the Fc is a wild type homodimer; the antigen-binding domain binds to domain 4 of HER2. This antibody is also referred to as a trastuzumab analog.

[0319] v792, is wild-type trastuzumab with a IgG1 hinge, where both HER2 binding domains are derived from trastuzumab in the Fab format, and the and the Fc region is a heterodimer having the mutations T350V_L351Y_F405A_Y407V in Chain A, and T350V_T366L_K392L_T394W Chain B; the antigen-binding domain binds to domain 4 of HER2. This antibody is also referred to as a trastuzumab analog.

[0320] v4184, a bivalent anti-HER2 antibody, where both HER2 binding domains are derived from pertuzumab in the Fab format, and the Fc region is a heterodimer having the mutations T350V_L351Y_F405A_Y407V in Chain A, and T350V_T366L_K392L_T394W Chain B. The antigen-binding domain binds to domain 2 of HER2. This antibody is also referred to as a pertuzumab analog.

[0321] hIgG, is a commercial non-specific polyclonal antibody control (Jackson ImmunoResearch, #009-000-003).

[0322] These antibodies and controls (other than human IgG) were cloned and expressed as follows. The genes encoding the antibody heavy and light chains were constructed via gene synthesis using codons optimized for human/mammalian expression. The Trastuzumab Fab sequence was generated from a known HER2/neu domain 4 binding antibody (Carter P. et al. (1992) Humanization of an anti p185 HER2 antibody for human cancer therapy. *Proc Natl Acad Sci* 89, 4285.) And the Fc was an IgG1 isotype. The scFv sequence was generated from the VH and VL domains of Trastuzumab using a glycine-serine linker (Carter P. et al. (1992) Humanization of an anti p185 her2 antibody for human cancer therapy. *Proc Natl Acad Sci* 89, 4285.). The Pertuzumab Fab sequence was generated from a known HER2/neu domain 2 binding Ab (Adams C W et al. (2006) Humanization of a recombinant monoclonal antibody to produce a therapeutic her dimerization inhibitor, Pertuzumab. *Cancer Immunol Immunother.* 2006; 55(6): 717-27).

[0323] The final gene products were sub-cloned into the mammalian expression vector PTT5 (NRC-BRI, Canada) and expressed in CHO cells (Durocher, Y., Perret, S. & Kamen, A. High-level and high-throughput recombinant protein production by transient transfection of suspension-growing CHO cells. *Nucleic acids research* 30, e9 (2002)).

[0324] The CHO cells were transfected in exponential growth phase (1.5 to 2 million cells/ml) with aqueous 1 mg/ml 25 kDa polyethylenimine (PEI, polysciences) at a PEI:DNA ratio of 2.5:1. (Raymond C. et al. A simplified polyethylenimine-mediated transfection process for large-scale and high-throughput applications. Methods. 55(1):44-51 (2011)). To determine the optimal concentration range for forming heterodimers, the DNA was transfected in optimal DNA ratios of the heavy chain a (HC-A), light chain (LC), and heavy chain B (HC-B) that allow for heterodimer formation (e.g. HC-A/HC-B/LC ratios=30:30:40 (v5019). Transfected cells were harvested after 5-6 days with the culture medium collected after centrifugation at 4000 rpm and clarified using a 0.45 μm filter.

[0325] The clarified culture medium was loaded onto a MabSelect SuRe (GE Healthcare) protein-A column and washed with 10 column volumes of PBS buffer at pH 7.2. The antibody was eluted with 10 column volumes of citrate buffer at pH 3.6 with the pooled fractions containing the antibody neutralized with TRIS at pH 11.

[0326] The protein-A antibody eluate was further purified by gel filtration (SEC). For gel filtration, 3.5 mg of the antibody mixture was concentrated to 1.5 mL and loaded onto a Sephadex 200 HiLoad 16/600 200 pg column (GE Healthcare) via an AKTA Express FPLC at a flow-rate of 1 mL/min. PBS buffer at pH 7.4 was used at a flow-rate of 1 mL/min. Fractions corresponding to the purified antibody were collected, concentrated to ~1 mg/mL.

[0327] Exemplary anti-HER2 ECD2×ECD4 biparatopic antibodies with different molecular formats (e.g. v6717, scFv-scFv IgG1; v6903 and v6902 Fab-Fab IgG1; v5019, v7091 and v10000 Fab-scFv IgG1) were cloned, expressed and purified as described above.

[0328] To quantify antibody purity and to determine the amount of target heterodimer protein and possible homodimer and/or half antibody and/or mispaired light chain contaminant, LC-MS intact mass analysis was performed. The LC-MS intact mass analysis was performed as described in Example 2, excluding DAR analysis calculations used for ADC molecules.

[0329] The data is shown in Table 2. Table 2 shows that expression and purification of these biparatopic antibodies resulted in 100% of the desired product for v6717, 91% of the desired heterodimeric product for v6903, and 62% of the desired product for v6902. The numbers in brackets indicate the quantities of the main peak plus a side peak of +81 Da. This side peak is typically detected with variants that contain C-terminal HA tags (such of v6903 and v6902). Adding the main and side peaks yields heterodimer purities of approximately 98% and 67% for v6903 and v6903. Based on the high heterodimer purity, v6903 was identified as the representative Fab-Fab anti-HER2 biparatopic variant for direct comparison to the scFv-scFv and Fab-scFv formats. v6903 was included in all format comparison assays.

TABLE 2

Expression and purification of antibodies

Variant	Desired heterodimer species (+side peak)
6717	100.0
6903	90.9 (97.7)
6902	62.4 (67.4)

Example 2: Preparation of Exemplary Anti-HER2 Biparatopic Antibody Drug Conjugates (ADCs)

[0330] The following anti-HER2 biparatopic antibody drug conjugates (anti-HER2 biparatopic-ADCs) were prepared. ADCs of variants 5019, 7091, 10000 and 506 were prepared. These ADCs are identified as follows:

[0331] v6363 (v5019 conjugated to DM1)

[0332] v7148 (v7091 conjugated to DM1)

[0333] v10553 (v10000 conjugated to DM1)

[0334] v6246 (v506 conjugated to DM1, analogous to T-DM1, trastuzumab-emtansine)

[0335] v6249 (human IgG conjugated to DM1)

[0336] The ADCs were prepared via direct coupling to maytansine. Antibodies purified by Protein A and SEC, as described in Example 1 (>95% purity), were used in the preparation of the ADC molecules. ADCs were conjugated following the method described in Kovtun Y V, Audette C A, Ye Y, et al. Antibody-drug conjugates designed to eradicate tumors with homogeneous and heterogeneous expression of the target antigen. Cancer Res 2006; 66:3214-21. The ADCs had an average molar ratio of 3.0 maytansinoid molecules per antibody as determined by LC/MS and described below.

[0337] Details of the reagents used in the ADC conjugation reaction are as follows: Conjugation Buffer 1: 50 mM Potassium Phosphate/50 mM Sodium Chloride, pH 6.5, 2 mM EDTA. Conjugation Buffer 2: 50 mM Sodium Succinate, pH 5.0. ADC formulation buffer: 20 mM Sodium Succinate, 6% (w/v) Trehalose, 0.02% polysorbate 20, pH 5.0. Dimethylacetamide (DMA); 10 mM SMCC in DMA (prepared before conjugation), 10 mM DM1-SH in DMA (prepared before conjugation), 1 mM DTNB in PBS, 1 mM Cysteine in buffer, 20 mM Sodium Succinate, pH 5.0. UV-VIS spectrophotometer (Nano drop 100 from Fisher Scientific), PD-10 columns (GE Healthcare).

[0338] The ADCs were prepared as follows. The starting antibody solution was loaded onto the PD-10 column, previously equilibrated with 25 mL of Conjugation Buffer 1, followed by 0.5 ml Conjugation Buffer 1. The antibody eluate was collect and the concentration measured at A_{280} and the concentration was adjusted to 20 mg/mL. The 10 mM SMCC-DM1 solution in DMA was prepared. A 7.5 molar equivalent of SMCC-DM1 to antibody was added to the antibody solution and DMA was added to a final DMA volume of 10% v/v. The reaction was briefly mixed and incubated at RT for 2 h. A second PD-10 column was equilibrated with 25 ml of Conjugation Buffer 1 and the antibody-MCC-DM1 solution was added to the column follow by 0.5 ml of Buffer 1. The antibody-MCC-DM1 eluate was collected and the A_{252} and A_{280} of antibody solution was measured. The Antibody-MCC-DM1 concentration was calculated (□=1.45 $mg^{-1}cm^{-1}$, or 217500 $M^{-1}cm^{-1}$). The ADCs were analyzed on a SEC-HPLC column for high MW analysis (SEC-HPLC column TOSOH, G3000-SWXL, 7.8 mm×30 cm, Buffer, 100 mM Sodium phosphate, 300 mM Sodium Chloride, pH 7.0, flow rate: 1 ml/min).

[0339] ADC drug to antibody ratio (DAR) was analysed by HIC-HPLC_using the Tosoh TSK gel Butyl-NPR column (4.6 mm×3.5 mm×2.5 mm). Elution was performed at 1 ml/min using a gradient of 10-90% buffer B over 25 min followed by 100% buffer B for 4 min. Buffer A comprises 20 mM sodium phosphate, 1.5 M ammonium sulphate, pH 7.0. Buffer B comprises 20 mM sodium phosphate, 25% v/v isopropanol, pH 7.0.

[0340] ADC drug to antibody ratio (DAR) was determined by LC-MS by the following method. The antibodies were deglycosylated with PNGase F prior to loading on the LC-MS. Liquid chromatography was carried out on an Agilent 1100 Series HPLC under the following conditions:

[0341] Flow rate: 1 mL/min split post column to 100 uL/min to MS. Solvents: A=0.1% formic acid in ddH2O, B=65% acetonitrile, 25% THF, 9.9% ddH2O, 0.1% formic acid. Column: 2.1×30 mm PorosR2. Column Temperature: 80° C.; solvent also pre-heated. Gradient: 20% B (0-3 min), 20-90% B (3-6 min), 90-20% B (6-7 min), 20% B (7-9 min).

[0342] Mass Spectrometry (MS) was subsequently carried out on an LTQ-Orbitrap XL mass spectrometer under the following conditions: Ionization method using Ion Max Electrospray. Calibration and Tuning Method: 2 mg/mL solution of CsI is infused at a flowrate of 104/min. The Orbitrap was tuned on m/z 2211 using the Automatic Tune feature (overall CsI ion range observed: 1690 to 2800). Cone Voltage: 40V; Tube Lens: 115V; FT Resolution: 7,500; Scan range m/z 400-4000; Scan Delay: 1.5 min. A molecular weight profile of the data was generated using Thermo's Promass deconvolution software. Average DAR of the sample was determined as a function of DAR observed at each fractional peak (using the calculation: (DAR×fractional peak intensity)).

[0343] Table 3 summarizes the average DAR for the ADC molecules. The average DAR for the exemplary anti-HER2 biparatopic antibody and control was approximately 3.

TABLE 3

Average DAR for ADCs

	DAR (LC-MS)	DAR (HIC)	n
v6246	2.9	3.0	5
v6363	2.6	3.3	5
v7148	3.4	3.9	1
v10553	4.0	4.0	1

Example 3: Expression and Bench-Scale Purification of Anti-HER2 Biparatopic Antibody

[0344] The anti-HER2 biparatopic antibodies (v5019, v7091 and v10000) described in Example 1 were expressed in 10 and/or 25 L volumes and purified by protein A and size exclusion chromatography (SEC) as follows.

[0345] The clarified culture medium was loaded onto a MabSelect SuRe (GE Healthcare) protein-A column and washed with 10 column volumes of PBS buffer at pH 7.2. The antibody was eluted with 10 column volumes of citrate buffer at pH 3.6 with the pooled fractions containing the antibody neutralized with Tris at pH 11.

[0346] The protein-A antibody eluate was further purified by gel filtration (SEC). For gel filtration, 3.5 mg of the antibody mixture was concentrated to 1.5 mL and loaded onto a Sephadex 200 HiLoad 16/600 200 pg column (GE Healthcare) via an AKTA Express FPLC at a flow-rate of 1 mL/min. PBS buffer at pH 7.4 was used at a flow-rate of 1 mL/min. Fractions corresponding to the purified antibody were collected, concentrated to ~1 mg/mL. The purified proteins were analyzed by LC-MS as described in Example 2.

[0347] The results of the 10 L expression and bench-scale protein A and SEC purification are shown in FIGS. **2**A and **2**B. FIG. **2**A shows the SEC chromatograph of the protein A purified v5019 and FIG. **2**B shows the non-reducing SDS-PAGE gel that compares the relative purity of a protein A pooled fraction as well as SEC fractions 15 and 19 and pooled SEC fractions 16-18. These results show that the anti-HER2 biparatopic antibody was expressed and that purification by protein A and SEC yielded a pure protein sample. Further quantification was performed by UPLC-SEC and LC-MS analysis and is described in Example 4.

[0348] The results of the 25 L expression and bench-scale protein A purification is shown in FIG. **2**C. FIG. **2**C shows

SDS-PAGE gel that compares the relative purity of a protein A purified v10000. Lane M contains: protein marker; lane 1 contains: v10000 under reducing conditions; lane 2 contains v10000 under non-reducing conditions. The SDS-PAGE gel shows that v10000 is pure and runs at the correct predicted MW of approximately 125 kDa under non-reducing conditions. Under reducing conditions two heavy chains bands are visible corresponding to the CH-A heavy chain (approximately 49 kDa) and the CH-B heavy chain (approximately 52.5 kDa); the CH-A light chain is visible and runs at the correct predicted mass of approximately 23.5 kDa. These results show that the anti-HER2 biparatopic antibody was expressed and that one-step purification by protein A yielded a pure protein sample. Further quantification was performed by UPLC-SEC and LC-MS analysis and is described in Example 4.

Example 4: Analysis of Biparatopic Anti-HER2 Antibody Purity by UPLC-SEC and LC-MS

[0349] The purity and percent aggregation of exemplary protein A and SEC purified biparatopic anti-HER2 heteromultimers was determined by UPLC-SEC by the method described.

[0350] UPLC-SEC analysis was performed using a Waters BEH200 SEC column set to 30° C. (2.5 mL, 4.6×150 mm, stainless steel, 1.7 μm particles) at 0.4 ml/min. Run times consisted of 7 min and a total volume per injection of 2.8 mL with running buffers of 25 mM sodium phosphate, 150 mM sodium acetate, pH 7.1; and, 150 mM sodium phosphate, pH 6.4-7.1. Detection by absorbance was facilitated at 190-400 nm and by fluorescence with excitation at 280 nm and emission collected from 300-360 nm. Peak integration was analyzed by Empower 3 software.

[0351] UPLC-SEC results of the pooled v5019 SEC fractions are shown in FIG. **3**A. These results indicate that the exemplary anti-HER2 biparatopic antibody was purified to >99% purity with less than 1% HMW species by protein A and SEC chromatography.

[0352] UPLC-SEC results of the v10000 pooled Protein A fractions are shown in FIG. **3**B. These results indicate that the exemplary anti-HER2 biparatopic antibody was purified to >96% purity with less than 1% HMW species by protein A chromatography.

[0353] The purity of exemplary biparatopic anti-HER2 antibodies was determined using LC-MS under standard conditions by the method described in Example 2. Results from LC-MS analysis of the pooled SEC fractions of v5019 are shown in FIG. **4**A. This data shows that the exemplary biparatopic anti-HER2 heterodimer has a heterodimer purity of 100%. Results from LC-MS analysis of the pooled protein A fractions of v10000 are shown in FIG. **4**B. This data shows that the exemplary biparatopic anti-HER2 heterodimer has a heterodimer purity of 98% following a one-step protein A purification.

[0354] Antibodies purified by protein A chromatography and/or protein A and SEC were used for the assays described in the following Examples.

Example 5. Large-Scale Expression and Manufacturability Assessment of Biparatopic Anti-HER2 Antibody Purified by Protein A and CEX Chromatography

[0355] The exemplary anti-HER2 biparatopic antibody v5019 described in Example 1 was expressed in a 25 L scale and purified as follows.

[0356] Antibody was obtained from supernatant followed by a two-step purification method that consisted of Protein A purification (MabSelect™ resin; GE Healthcare) followed by cation exchange chromatography (HiTrap™ SP FF resin; GE Healthcare) by the protocol described.

[0357] CHO-3E7 cells were maintained in serum-free Freestyle CHO expression medium (Invitrogen, Carlsbad, Calif., USA) in Erlenmeyer Flasks at 37° C. with 5% CO2 (Corning Inc., Acton, Mass.) on an orbital shaker (VWR Scientific, Chester, Pa.). Two days before transfection, the cells were seeded at an appropriate density in a 50 L CellBag with a volume of 25 L using the Wave Bioreactor System 20/50 (GE Healthcare Bio-Science Corp). On the day of transfection, DNA and PEI (Polysciences, Eppelheim, Germany) were mixed at an optimal ratio and added to the cells using the method described in Example 1. Cell supernatants collected on day 6 was used for further purification.

[0358] Cell culture broth was centrifuged and filtered before loading onto 30 mL Mabselect™ resin packed in XK26/20 (GE Healthcare, Uppsala, Sweden) at 10.0 mL/min. After washing and elution with appropriate buffer, the fractions were collected and neutralized with 1 M Tris-HCl, pH 9.0. The target protein was further purified via 20 mL SP FF resin packed in XK16/20 (GE Healthcare, Uppsala, Sweden). MabSelect™ purified sample was diluted with 20 mM NaAC, pH5.5 to adjust the conductivity to <5 ms/cm and 50 mM citrate acid (pH3.0) was added adjust the sample pH value to 5.5. Sample was loaded at a 1 mL/min onto the HiTrap™ SP FF resin (GE Healthcare) and washed with 20 mM NaAC. Protein was eluted using a gradient elution 0-100% of 20 mM NaAC, 1 M NaCl, pH5.5, 10 CV at 1 mL/min.

[0359] The purified protein was analyzed by SDS-PAGE as described in Example 1, and LC-MS for heterodimer purity by the method described in example 4. The results are shown in FIGS. **5**A and **5**B. FIG. **5**A shows the SDS-PAGE results of v5019 following MabSelect™ and HiTrap™ SP FF purification; lane M contains: protein marker; lane 1: v5019 under reducing conditions (3 μg); Lane 2: v5019 under non-reducing conditions (2.5 μg). The SDS-PAGE gel shows that v5019 is relatively pure following MabSelect™ and HiTrap™ SP FF purification and, under non-reducing conditions, runs at the correct predicted MW of approximately 125 kDa. Under reducing conditions two heavy chains bands are visible corresponding to the CH-A heavy chain (approximately 49 kDa) and the CH-B heavy chain (approximately 52.5 kDa); the CH-A light chain is visible and runs at the correct predicted mass of approximately 23.5 kDa.

[0360] LC-MS analysis of the MabSelect™ and HiTrap™ SP FF purified v5019 was performed to determine heterodimer purity using the method described in Example 4. Results from the LC-MS analysis are shown in FIG. **5**B. These results show that v5019 purification using MabSelect™ and HiTrap™ SP FF yields protein with >99% heterodimer purity and with little (<1%) or undetectable homodimer or half antibody contamination.

Example 6: Comparison of Bmax of a Biparatopic Anti-HER2 Antibody Against Bmax of Controls in Cell Lines Expressing Low to High Levels of HER2

[0361] The following experiment was performed to measure the ability of an exemplary biparatopic anti-HER2

antibody to bind to cells expressing varying levels of HER2 in comparison to controls. The cell lines used were SKOV3 (HER2 2+/3+), JIMT-1 (HER2 2+), MDA-MB-231 (HER2 0/1+), and MCF7 (HER2 1+). The biparatopic anti-HER2 antibodies tested include v5019, v7091 and v10000. The ability of the biparatopic anti-HER2 antibodies to bind to the HER2 expressing (HER2+) cells was determined as described below, with specific measurement of B_{max} and apparent K_D (equilibrium dissociation constant).

[0362] Binding of the test antibodies to the surface of HER2+ cells was determined by flow cytometry. Cells were washed with PBS and resuspended in DMEM at 1×10^5 cells/100 μl. 100 μl cell suspension was added into each microcentrifuge tube, followed by 10 μl/tube of the antibody variants. The tubes were incubated for 2 hr 4° C. on a rotator. The microcentrifuge tubes were centrifuged for 2 min 2000 RPM at room temperature and the cell pellets washed with 500 μl media. Each cell pellet was resuspended 100 μl of fluorochrome-labelled secondary antibody diluted in media to 2 μg/sample. The samples were then incubated for 1 hr at 4° C. on a rotator. After incubation, the cells were centrifuged for 2 min at 2000 rpm and washed in media. The cells were resuspended in 500 μl media, filtered in tube containing 5 μl propidium iodide (PI) and analyzed on a BD LSR II flow cytometer according to the manufacturer's instructions. The K_D of exemplary biparatopic anti-HER2 heterodimer antibody and control antibodies were assessed by FACS with data analysis and curve fitting performed in GraphPad Prism.

[0363] The results are shown in FIGS. **6**A-**6**G. These results demonstrate that exemplary biparatopic anti-HER2 antibodies (v5019, v7091 and v10000) can bind to HER2+ cells with approximately a 1.5-fold higher Bmax compared to an anti-HER2 FSA (v506). The results in FIG. **6**A-**6**G also show that biparatopic anti-HER2 antibodies (v5019, v7091 and v10000) can bind to HER2+ cells with a similar Bmax compared to a combination of two anti-HER2 FSAs (v506+v4184).

[0364] The binding results for HER2+ SKOV3 cells (HER2 2/3+) are shown in FIGS. **6**A, **6**E and Table 4 and Table 5. The results in FIG. **6**A and Table 4 show that exemplary biparatopic anti-HER2 antibody (v5019) displays approximately a 1.5-fold higher Bmax in binding to SKOV3 cells compared to two different anti-HER2 FSAs (v506 or v4184). The results also show that exemplary biparatopic anti-HER2 antibody (v5019) displays equivalent Bmax compared to the combination of two anti-HER2 FSAs (v506+v4184). The apparent K_D of v5019 for binding to SKOV3 was approximately 2 to 4-fold higher compared to either anti-HER2 FSA alone (v506 or v4184), or the combination of two anti-HER2 FSAs (v506+v4184).

TABLE 4

Binding to SKOV3 cells

Antibody variant	K_D (nM)	Bmax
v506	2.713	29190
v4184	4.108	29204
v5019	8.084	47401
v506 + v4184	4.414	49062

[0365] The results in FIG. **6**E and Table 5 show that exemplary biparatopic anti-HER2 antibodies (v5019, 7091 and v10000) display approximately a 1.5 to 1.6-fold higher Bmax in binding to SKOV3 cells compared to two different anti-HER2 FSAs (v506 or v4184). The results also show that exemplary biparatopic anti-HER2 antibodies (v5019, 7091 and v10000) display equivalent Bmax compared to the combination of two anti-HER2 FSAs (v506+v4184). The apparent K_D of v5019, v7091, v10000 and the combination of two anti-HER2 FSAs (v506+v4184) for binding to SKOV3 was approximately 2 to 3-fold higher compared to either anti-HER2 FSA alone (v506 or v4184).

TABLE 5

Binding to SKOV3

Antibody Variant	K_D (nM)	Bmax
v506	4.8	30007
v4184	5.6	27628
v506 + v4184	10.0	49014
v5019	13.6	47693
v7091	14.5	44737
v10000	10.3	48054

[0366] Binding curves in the JIMT-1 cell line (HER2 2+) are shown in FIG. **6**B and Table 6. These results show that exemplary biparatopic anti-HER2 antibody (v5019) displays approximately a 1.5-fold higher Bmax in binding to JIMT-1 cells compared to an anti-HER2 FSAs (v506). The results also show that exemplary biparatopic anti-HER2 antibody (v5019) displays equivalent Bmax compared to the combination of two anti-HER2 FSAs (v506+v4184). The apparent K_D of v5019 for binding to JIMT-1 was approximately 2-fold higher compared to the anti-HER2 FSA (v506), and was similar (approximately 1.2 fold greater) compared to the combination of two anti-HER2 FSAs (v506+v4184).

TABLE 6

Binding to JIMT-1 cells

Antibody variant	K_D (nM)	Bmax
v506	1.875	4905
v5019	4.317	7203
v506 + v4184	5.057	7200

[0367] Binding curves in the MCF7 cell line (HER2 1+) are shown in FIG. **6**C, **6**F and Tables 7 and 8. These results show that exemplary biparatopic anti-HER2 antibodies (v5019, 7091 and v10000) display approximately a 1.5-fold higher Bmax in binding to MCF7 cells compared to an anti-HER2 FSAs (v506). The results in FIG. **6**C also show that exemplary biparatopic anti-HER2 antibody (v5019) displays equivalent Bmax compared to the combination of two anti-HER2 FSAs (v506+v4184). The apparent K_D of v5019 for binding to MCF7 was similar to the anti-HER2 FSA (v506) and the combination of two anti-HER2 FSAs (v506+v4184).

TABLE 7

Binding to MCF7 cells

Antibody variant	K_D (nM)	Bmax
v506	1.301	542
v5019	1.506	872
v506 + v4184	2.095	903

The results in FIG. **6**F and Table 8 show that exemplary biparatopic anti-HER2 antibodies (v5019, v7091 and v10000) display approximately 1.6 to 1.7-fold greater Bmax compared to the FSA monospecific v506. The apparent K_D of v5019, v7091 and v10000 was similar to the anti-HER2 FSA (v506).

TABLE 8

Binding to MCF7 cells

Antibody Variant	K_D (nM)	Bmax
v506	3.5	571
v5019	5.6	968
v7091	6.5	918
v10000	3.7	915

[0368] Binding curves in the MDA-MB-231 cell line (HER2 0/1+) are shown in FIG. **6**D and Table 9. These results show that exemplary biparatopic anti-HER2 antibody (v5019) displays approximately a 1.5-fold higher Bmax in binding to MDA-MB-231 cells compared to an anti-HER2 FSA (v506). The results also show that exemplary biparatopic anti-HER2 antibody (v5019) displays equivalent Bmax compared to the combination of two anti-HER2 FSAs (v506+v4184). The apparent K_D of v5019 for binding to MDA-MB-231 was approximately 2.4-fold lower compared to the anti-HER2 FSA (v506) and was approximately 1.7-fold higher compared to the combination of two anti-HER2 FSAs (v506+v4184).

TABLE 9

Binding to MDA-MB-231 cells

Antibody variant	K_D (nM)	Bmax
v506	8.364	0.9521
v5019	3.543	1.411
v506 + v4184	2.040	1.542

[0369] Binding curves in the WI-38 lung fibroblast cell line are shown in FIG. **6**G and Table 10. The WI-38 cell line is a normal lung epithelium that expresses basal levels (HER2 0+, ~10,000 receptors/cell) of HER2 (Carter et al. 1992, PNAS, 89:4285-4289; Yarden 2000, HER2: Basic Research, Prognosis and Therapy). These results show that exemplary biparatopic anti-HER2 antibodies (v5019, v7091, v10000) displays equivalent cell surface decoration (Bmax) in binding to WI-38 cells compared to an anti-HER2 FSAs (v506); however, note that binding for v506 did not appear to reach saturation, and thus KD could not be determined. The apparent K_D among the exemplary biparatopic anti-HER2 antibodies was equivalent.

TABLE 10

Binding to WI-38 cells

Antibody Variant	K_D (nM)	Bmax
v506	Not determined	~366
v5019	7.0	380
v7091	8.3	371
v10000	8.4	418

[0370] These results show that an exemplary biparatopic anti-HER2 antibody can bind to HER2 1+, 2+ and 3+ tumor cells to levels that are approximately 1.5 to 1.6-fold greater than an anti-HER2 monospecific FSA, and that exemplary biparatopic anti-HER2 antibodies can bind to HER2 1+, 2+ and 3+ tumor cells to equivalent levels compared to the combination of two unique monospecific anti-HER2 FSAs with different epitope specificities. These results also show that the biparatopic anti-HER2 antibodies do not show increased binding (i.e. compared to monospecific anti-HER2 antibody, v506) to basal HER2 expressing cells that express approximately 10,000 HER2 receptors/cell or less, and that a threshold for increased cell surface binding to the biparatopic anti-HER2 antibodies occurs when the HER2 receptor level is approximately >10,000 receptors/cell. Based on this data it would be expected that the exemplary biparatopic anti-HER2 antibodies would have increased cell surface binding to HER2 3+, 2+ and 1+ tumor cells but would not have increased cell surface binding to non-tumor cells that express basal levels of the HER2 receptor at approximately 10,000 receptors or less.

Example 7: Ability of Biparatopic Anti-HER2 Antibody to Inhibit Growth of HER2+ Cells

[0371] The ability of an exemplary biparatopic anti-HER2 antibody to inhibit growth of cells expressing HER2 at the 3+ and 2+ level was measured. The experiment was carried out in the HER2 3+ cell lines BT-474, SKBr3, SKOV3, and HER2 2+ JIMT-1. The biparatopic anti-HER2 antibodies v5019, v7091 and v10000 were tested. The ability of the biparatopic anti-HER2 antibodies to inhibit the growth of BT-474 cells (200 nM antibody); SKOV3, SKBr3 and JIMT-1 cells (300 nM antibody) was measured as described below.

[0372] Test antibodies were diluted in media and added to the cells at 10 μl/well in triplicate. The plates were incubated for 3 days 37° C. Cell viability was measured using either AlamarBlue™ (Biosource # dal1100), or CelltiterGlo® and absorbance read as per the manufacturer's instructions. Data was normalized to untreated control and analysis was performed in GraphPad prism.

[0373] The growth inhibition results are shown in FIG. **7**A-E. A summary of the results is provided in Tables 11A and 11B. The results FIGS. **7**A-B and Table 11A indicate that exemplary anti-HER2 biparatopic (v5019) is capable of growth inhibition of HER2+ SKOV3 and BT-474 cell lines. FIG. **10**A shows that anti-HER2 biparatopic antibody mediated the greatest growth inhibition of SKOV3 when compared to anti-HER2 FSA (v506) and when compared to the combination of two anti-HER2 FSA antibodies (v506+v4184).

TABLE 11A

Growth Inhibition of HER2 3+ Cancer Cells

	% Survival	
Treatment	SKOV3 HER2 2+/3+	BT-474 HER2 3+
v506	88	37
v506 + v4184	96	32
v5019	77	43

[0374] The results in FIGS. **7**C-E and Table 11B indicate that exemplary anti-HER2 biparatopic antibodies (v5019, v7091 and v10000) can inhibit growth of HER2 3+ SKBR3, HER2 2+/3+ SKOV3, and HER2 2+ JIMT-1 tumor cell lines. FIG. **7**C shows that anti-HER2 biparatopic antibodies v7091 and v10000 mediated the greatest growth inhibition of HER2 3+ SKBr3 breast tumor cells. FIG. **7**D shows that anti-HER2 biparatopic antibodies (v7091 and v10000) mediated the greatest growth inhibition of HER2 3+ SKOV3 ovarian tumor cells. FIG. **7**E shows that anti-HER2 biparatopic antibodies (v7091 and v10000) mediated the greatest growth inhibition of HER2 2+ Herceptin-resistant JIMT-1 tumor cells. In all cell lines tested, exemplary anti-HER2 biparatopic antibodies (v7091 and v10000) mediated greater growth inhibition compared to the anti-HER2 FSA monospecific antibody (v506).

TABLE 11B

Growth inhibition of HER2 3+ Cancer Cells

	% Survival		
Treatment	SKBr3 HER2 3+	SKOV3 HER2 2+/3+	JIMT-1 HER2 2+
v506	52	107	107
v5019	59	83	106
v7091	35	79	85
v10000	34	73	84

[0375] These results show that exemplary saturating concentrations of biparatopic anti-HER2 antibodies can growth inhibit HER2 3+ and 2+ breast and ovarian and HER2 2+ Trastuzumab resistant tumor cells approximately 20% greater than a FSA anti-HER2 monospecific antibody.

Example 8: Preferential Binding of Paratopes of Biparatopic Anti-HER2 Antibodies to Dimeric HER2 Compared to HER2 ECD

[0376] This experiment was performed to determine the ability of the individual paratopes of exemplary biparatopic anti-HER2 antibodies to bind to dimeric HER2 and the HER2 ECD as a surrogate for differential binding between membrane bound HER2 (HER2-Fc) and the shed HER2 ECD. The experiment was carried out as follows.

[0377] Surface plasmon resonance (SPR) analysis: affinity of monovalent anti-HER2 antibodies (v1040 or v4182) for binding to the HER2 extracellular domain (sHER-2, Ebioscience BMS362, encoding amino acid 23-652 of the full length protein) and HER2-Fc (dimeric HER2-Fc fusion encoding the amino acid 1-652 of the extracellular domain; Sino Biological Inc., 10004-H02H) was measured by SPR using the T200 system from Biacore (GE Healthcare). Binding to the HER2 ECD was determined by the following method. HER2 ECD in 10 mm Hepes pH 6.8, was immobilized on CMS chip through amine coupling to a level of 44 RU (response units). Monovalent anti-HER2 antibodies were passed over the surface of the HER2 immobilized chip at concentrations ranging from 0.76-60 nM. Binding to the HER2-Fc was determined by the following method. HER2-Fc in 10 mm Hepes pH 6.8, was immobilized on CMS chip through amine coupling to a level of 43 RU. Monovalent anti-HER2 antibodies were passed over the surface of the HER2 immobilized chip at concentrations ranging from 0.76-60 nM. Antibody concentrations were analyzed for binding in triplicate. Equilibrium dissociation binding constants (K_D) and kinetics (ka and kd) were determined using the single cycle kinetics method. Sensograms were fit globally to a 1:1 Langmuir binding model. All experiments were conducted at room temperature.

[0378] Results are shown in FIG. **8**A, FIG. **8**B, Table 11C and Table 11D. The results in FIG. **8**A and Table 11C show SPR binding data of the monovalent anti-HER2 antibody (v1040; representing the antigen-binding domain on CH-B of exemplary anti-HER2 biparatopic antibody). FIG. **8**A illustrates the K_D values (nM) of v1040 binding to immobilized HER2 ECD or HER2-Fc and shows that monovalent anti-HER2 antibody has a lower K_D for binding to the HER2-Fc compared to the HER2 ECD. Table 11C shows the ka (1/M s) and kd (1/s) values of the monovalent anti-HER2 antibody (OA) compared to the full-sized anti-HER2 antibody (FSA) in binding to the HER2 ECD and HER2-FC ('HER2 mem'). This data shows comparable on (ka) and off (kd) rates of the OA and FSA for binding to the HER2 ECD and HER2-Fc.

TABLE 11C

ka (1/M s) and kd (1/s) values of the monovalent anti-HER2 antibody (OA) compared to the full-sized anti-HER2 antibody (FSA) in binding to the HER2 ECD and HER2-FC ('HER2 mem'

	ka (1/Ms)	kd (1/s)
OA vs. HER2 ECD	2.00E+05	6.15E−05
FSA vs. HER2 ECD	4.14E+05	2.01E−05
OA vs. HER2 mem	1.88E+05	4.38E−05
FSA vs. HER2 mem	3.41E+05	4.94E−06*

[0379] Results in FIG. **8**B and Table 11D show the SPR binding data of the monovalent anti-HER2 antibody (v4182; representing the antigen-binding domain on CH-A of exemplary anti-HER2 biparatopic antibody). FIG. **8**B illustrates the K_D values (nM) of v4182 binding to immobilized HER2 ECD or HER2-Fc and shows that monovalent anti-HER2 antibody has a lower K_D for binding to the HER2-Fc compared to the HER2 ECD. Table 11D shows the ka (1/M s) and kd (1/s) values of the monovalent anti-HER2 antibody (OA) compared to the full-sized anti-HER2 antibody (FSA) in binding to the HER2 ECD and HER2-FC ('HER2 mem'). This data shows comparable on rates (ka) and off rates (kd) of the OA and FSA for binding to the HER2 ECD and HER2-Fc.

TABLE 11D

	ka (1/Ms)	kd (1/s)
OA vs. HER2 ECD	9.08E+04	6.17E−04
FSA vs. HER2 ECD	9.55E+04	3.93E−04
OA vs. HER2 mem	1.39E+05	2.04E−04
FSA vs. HER2 mem	1.77E+05	6.84E−05

[0380] These data show that each of the paratopes of the exemplary anti-HER2 biparatopic antibody have lower K_D values for binding to the dimeric HER2 antigen, a representative of membrane bound HER2, as compared to the HER2 ECD. Based on this data it would be expected that the exemplary anti-HER2 antibody would have a higher binding affinity for the membrane bound HER2 antigen as compared to the shed HER2 ECD that is present in the serum of diseased patients and can act as a sink for the therapeutic antibody (Brodowicz T, et al. Soluble HER-2/neu neutral-

izes biologic effects of anti-HER-2/neu antibody on breast cancer cells in vitro. Int J Cancer. 1997; 73:875-879). For example, baseline HER2 ECD levels≤15 ng/mL; whereas patients with progressive disease have HER2 ECD≥38 ng/mL.

Example 9: Whole Cell Loading and Internalization of Biparatopic Anti-HER2 Antibody in HER2+ Cells

[0381] This experiment was performed to assess the ability of an exemplary biparatopic anti-HER2 antibody to be internalized in HER2 2+ cells. The direct internalization method was followed according to the protocol detailed in Schmidt, M. et al., *Kinetics of anti-carcinoembryonic antigen antibody internalization: effects of affinity, bivalency, and stability*. Cancer Immunol Immunother (2008) 57:1879-1890. Specifically, the antibodies were directly labeled using the AlexaFluor® 488 Protein Labeling Kit (Invitrogen, cat. no. A10235), according to the manufacturer's instructions.

[0382] For the internalization assay, 12 well plates were seeded with 1×10^5 cells/well and incubated overnight at 37° C.+5% CO2. The following day, the labeled antibodies were added at 200 nM in DMEM+10% FBS and incubated 24 hours at 37° C.+5% CO2. Under dark conditions, media was aspirated and wells were washed 2×500 μL PBS. To harvest cells, cell dissociation buffer was added (250 μL) at 37° C. Cells were pelleted and resuspended in 100 μL DMEM+10% FBS without or with anti-Alexa Fluor 488, rabbit IgG fraction (Molecular Probes, A11094) at 50 μg/mL, and incubated on ice for 30 min. Prior to analysis 300 μL DMEM+10% FBS the samples filtered 4 μl propidium iodide was added. Samples were analyzed using the LSRII flow cytometer.

[0383] The ability of exemplary anti-HER2 biparatopic antibody to internalize in HER2+ cells is shown in FIG. **9**A and FIG. **9**B. FIG. **9**A shows the results of detectable surface and internal antibody in BT-474 cells following 24 h incubation with the exemplary anti-HER2 biparatopic antibody and anti-HER2 FSA control. These results show that incubation with exemplary anti-HER2 biparatopic antibody (v5019) results in approximately 2-fold more internalized antibody in BT-474 cells compared to the anti-HER2 FSA control. FIG. **9**B shows the results of detectable surface and internal antibody in JIMT-1 cells following 24 h incubation with the exemplary anti-HER2 biparatopic antibody and anti-HER2 FSA control. These results show that incubation with exemplary anti-HER2 biparatopic antibody (v5019) results in approximately 2-fold more internalized antibody in JIMT-1 cells compared to the anti-HER2 FSA control. The amount of surface staining post 24 h was comparable among the biparatopic anti-HER2 and anti-HER2 FSA in both BT-474 and JIMT-1 cells.

[0384] The results in FIG. **10**A-F show a comparison of detectable antibody bound to the surface of whole cells after 2 h at 4° C., compared to antibody bound to the surface following incubation for 24 h at 37° C.; in addition to the amount of internalized antibody following 24 h at 37° C. FIG. **10**A shows the results in BT-474 cells following incubation with the exemplary anti-HER2 biparatopic antibody and anti-HER2 FSA control. These results show that incubation of exemplary anti-HER2 biparatopic antibody with BT-474 cells for 24 h results in approximately a 15% reduction of antibody detected on the surface of whole cells. FIG. **10**A also shows that incubation with exemplary anti-HER2 biparatopic antibody (v5019) results in approximately 2-fold more internalized antibody in BT-474 cells compared to the anti-HER2 FSA control.

[0385] FIG. **10**B shows the results in JIMT-1 cells following incubation with the exemplary anti-HER2 biparatopic antibody and anti-HER2 FSA control. FIG. **10**B is a repeat of the experiment shown in FIG. **9**B with the addition of surface staining following 2 h at 4° C. These results show that incubation of exemplary anti-HER2 biparatopic antibody with JIMT-1 cells for 24 h results in approximately a 57% reduction of antibody detected on the surface of whole cells. FIG. **10**B also shows that incubation with exemplary anti-HER2 biparatopic antibody (v5019) results more internalized antibody in BT-474 cells following 24 incubation at 37° C., compared to the anti-HER2 FSA control.

[0386] FIG. **10**C shows the results in SKOV3 cells following incubation with the exemplary anti-HER2 biparatopic antibody. These results show that incubation of exemplary anti-HER2 biparatopic antibody with SKOV3 cells for 24 h results in approximately a 32% reduction of antibody detected on the surface of whole cells.

[0387] FIG. **10**D shows the results in MCF7 cells following incubation with the exemplary anti-HER2 biparatopic antibody. These results show that incubation of exemplary anti-HER2 biparatopic antibody with MCF7 cells for 24 h results in approximately a 45% reduction of antibody detected on the surface of whole cells.

[0388] FIG. **10**E shows the results in SKOV3 cells following incubation with the exemplary anti-HER2 biparatopic antibodies, v5019, v7091 and v10000. These results show that incubation of exemplary anti-HER2 biparatopic antibodies results in 1.5 to 1.8-fold more internalized antibody with SKOV3 cells compared to the anti-HER2 FSA control. Incubation with the anti-HER2 FSA control for 24 h resulted in the greatest reduction (~77%) of antibody detected on the surface of whole cells.

[0389] FIG. **10**F shows the results in JIMT-1 cells following incubation with the exemplary anti-HER2 biparatopic antibodies, v5019, v7091 and v10000. These results show that incubation of exemplary anti-HER2 biparatopic antibodies results in 1.4 to 1.8-fold more internalized antibody with JIMT-1 cells compared to the anti-HER2 FSA control. Incubation with the anti-HER2 biparatopic antibodies (v5019 and v10000) for 24 h resulted in the greatest reduction (~64%) of antibody detected on the surface of whole cells.

[0390] These results show that exemplary anti-HER2 biparatopic antibodies have superior internalization properties in HER2+ cells compared to a monospecific anti-HER2 FSA. The reduction of surface antibody detected following 24 h incubation at 37° C. shows that an exemplary anti-HER2 biparatopic antibody is capable of reducing the amount of cell surface HER2 receptor following incubation in HER2+ cells and that surface HER2 reduction post incubation is greatest in HER2 2+ tumor cells.

Example 10: Cellular Staining and Location of an Anti-HER2 Biparatopic Antibody Following Incubation with HER2+ Cells at 1, 3 and 16 Hours

[0391] This experiment was performed to analyze internalization of the exemplary anti-HER2 biparatopic antibody in HER2+ JIMT-1 cells at different time points and as an orthogonal method to that presented in Example 9 to analyze whole cell loading and internalization.

[0392] JIMT-1 cells were incubated with the antibody (v506, v4184, v5019, or a combination of v506 and v4184) at 200 nM in serum-free DMEM, 37° C.+5% CO_2 for 1h, 3h and 16h. Cells were gently washed two times with warmed sterile PBS (500 ml/well). Cells were fixed with 250 ml of 10% formalin/PBS solution for 10 min at RT. The fixed cells were washed three times with PBS (500 μl/well), permeabilized with 250 μl/well of PBS containing 0.2% Triton X-100 for 5 min, and washed three times with 500 μl/well PBS. Cells were blocked with 500 μl/well of PBS+5% goat serum for 1 h at RT. Blocking buffer was removed, and 300 μl/well secondary antibody (Alexa Fluor 488-conjugated AffiniPure Fab Fragment Goat anti-Human IgG (H+L); Jackson ImmunoResearch Laboritories, Inc.; 109-547-003) was incubated for 1 h at RT. Cells were washed three times with 500 μl/well of PBS and the coverslips containing fixed cells were then mounted on a slide using Prolong gold anti-fade with DAPI (Life Technologies; #P36931). 60× single images were acquired using Olympus FV1000 Confocal microscope.

[0393] The results indicated that the exemplary anti-HER2 biparatopic antibody (v5019) was internalized into JIMT-1 cells at 3 h and was primarily located close to the nuclei. Comparing images at the 3h incubation showed a greater amount of internal staining associated with the anti-HER2 biparatopic antibody compared to the combination of two anti-HER2 FSAs (v506+v4184) and compared to the individual anti-HER2 FSA (v506 or v4184). Differences in the cellular location of antibody staining were seen when the anti-HER2 biparatopic antibody (v5019) results were compared with the anti-HER2 FSA (v4184); where the anti-HER2 FSA (v4184) showed pronounced plasma membrane staining at the 1, 3 and 16 h time points. The amount of detectable antibody was reduced at the 16 h for the anti-HER2 FSA (v506), the combination of two anti-HER2 FSAs (v506+v4184) and anti-HER2 biparatopic antibody treatments (data not shown).

[0394] These results show that the exemplary anti-HER2 biparatopic antibody v5019 was internalized in HER2+ cells and the internalized antibody was detectable after 3 h incubation. These results are consistent with the results presented in Example 9 that show exemplary anti-HER2 biparatopic antibody can internalize to greater amounts in HER2+ cells compared to an anti-HER2 FSA.

Example 11: ADCC of HER2+ Cells Mediated by Biparatopic Anti-HER2 Antibody Compared to Controls

[0395] This experiment was performed in order to measure the ability of an exemplary biparatopic anti-HER2 antibody to mediate ADCC in SKOV3 cells (ovarian cancer, HER2 2+/3+).

[0396] Target cells were pre-incubated with test antibodies (10-fold descending concentrations from 45 μg/ml) for 30 min followed by adding effector cells with effector/target cell ratio of 5:1 and the incubation continued for 6 hours at 37° C.+5% CO_2. Samples were tested with 8 concentrations, 10 fold descending from 45 μg/ml. LDH release was measured using LDH assay kit.

[0397] Dose-response studies were performed with various concentrations of the samples with a effector/target (E/T) ratios of 5:1. 3:1 and 1:1. Half maximal effective concentration (EC_{50}) values were analyzed with the sigmoidal dose-response non-linear regression fit using GraphPad prism.

[0398] Cells were maintained in McCoy's 5a complete medium at 37° C./5% CO_2 and regularly sub-cultured with suitable medium supplemented with 10% FBS according to protocol from ATCC. Cells with passage number fewer than p10 were used in the assays. The samples were diluted to concentrations between 0.3-300 nM with phenol red free DMEM medium supplemented with 1% FBS and 1% pen/strep prior to use in the assay.

[0399] The ADCC results in HER2+ SKOV3 cells at an effector to target cell ratio of 5:1 are shown in FIG. **11**A and Table 12. These results show that the exemplary biparatopic anti-HER2 antibody (v5019) mediated the greatest percentage of maximum target cell lysis by ADCC when compared to the anti-HER2 FSA (v792) and combination of two different anti-HER2 FSAs (v792+v4184). The difference in maximum cell lysis mediated by the exemplary biparatopic anti-HER2 antibody was approximately 1.6-fold greater compared to the anti-HER2 FSA, and approximately 1.2-fold greater compared to a combination of two different anti-HER2 FSAs (v792+v4184).

TABLE 12

Antibody variant	EC_{50} (nM)	% Max Cell Lysis
v792	~0.032	17.82
v5019	~0.164	28.57
v792 + v4184	~0.042	23.85

[0400] The ADCC results in HER2+ SKOV3 cells at an effector to target cell ratio of 3:1 are shown in FIG. **11**B and Table 13. These results show that the exemplary biparatopic anti-HER2 antibody (v5019) mediated the greatest percentage of maximum target cell lysis by ADCC when compared to the anti-HER2 FSA (v792) and combination of two different anti-HER2 FSAs (v792+v4184). The difference in maximum cell lysis mediated by the exemplary biparatopic anti-HER2 antibody was approximately 1.3-fold greater compared to the anti-HER2 FSA, and approximately 1.8-fold greater compared to a combination of two different anti-HER2 FSAs (v792+v4184).

TABLE 13

Antibody variant	EC_{50} (nM)	% Max Cell Lysis
v792	1.064	16.9
v5019	~0.4608	22.3
v792 + v4184	~1.078	12.3

[0401] The ADCC results in HER2+ SKOV3 cells at an effector to target cell ratio of 1:1 are shown in FIG. **11**C and Table 14. These results show that the exemplary biparatopic anti-HER2 antibody (v5019) mediated the greatest percentage of maximum target cell lysis by ADCC when to compared to the anti-HER2 FSA (v792) and combination of two different anti-HER2 FSAs (v792+v4184). The difference in maximum cell lysis mediated by the exemplary biparatopic anti-HER2 antibody was approximately 1.8-fold greater compared to the anti-HER2 FSA, and approximately 1.13-fold greater compared to a combination of two different anti-HER2 FSAs (v792+v4184).

TABLE 14

Antibody variant	EC_{50} (nM)	% Max Cell Lysis
v792	1.429	7.529
v5019	~1.075	13.29
v792 + v4184	~0.1121	11.73

[0402] The results in FIG. **11** and Tables 12-14 show that the exemplary biparatopic HER2 antibody mediates the greatest ADCC of SKOV3 cells at different E:T ratios when compared to an anti-HER2 FSA and combination of two anti-HER2 FSAs. The observation of increased ADCC mediated by the anti-HER2 biparatopic antibody would be expected in HER2+ diseased patients who express variable and/or reduced circulating effector cells following chemotherapy (Suzuki E. et al. Clin Cancer Res 2007; 13:1875-1882). The observations in FIG. **11** are consistent with the whole cell binding Bmax data presented in Example 6, that shows an approximate 1.5-fold increase in cell binding to the exemplary anti-HER2 biparatopic antibody compared to the anti-HER2 FSA.

Example 12: Ability of Exemplary Anti-HER2 Antibody to Bind to HER2 ECD

[0403] An SPR assay was used to evaluate the mechanism by which an exemplary anti-HER2 biparatopic antibody binds to HER2 ECD; specifically, to understand whether both paratopes of one biparatopic antibody molecule can bind to one HER2 ECD (Cis binding; 1:1 antibody to HER2 molecules) or if each paratope of one biparatopic antibody can bind two different HER2 ECDs (Trans binding; 1:2 antibody to HER2 molecules). A representation of cis vs. trans binding is illustrated in FIG. **14**. The correlation between a reduced (slower) off-rate with increasing antibody capture levels (surface density) is an indication of Trans binding (i.e. one antibody molecule binding to two HER2 molecules.

[0404] Affinity and binding kinetics of the exemplary biparatopic anti-HER2 antibody (v5019) to recombinant human HER2 were measured and compared to that of monovalent anti-HER2 antibodies (v630 or v4182; comprising the individual paratopes of v5019) was measured by SPR using the T200 system from Biacore (GE Healthcare). Between 2000 and 4000 RU of anti-human Fc injected at concentration between 5 and 10 μg/ml was immobilized on a CMS chip using standard amine coupling. Monovalent anti-HER2 antibody (v630 or v4182) and exemplary biparatopic anti-HER2 antibody (v5019) were captured on the anti-human Fc (injected at concentration ranging 0.08 to 8 μg/ml in PBST, 1 min at 10 ul/min) at response levels ranging from 350-15 RU. Recombinant human HER2 was diluted in PBST and injected at starting concentration of either 120 nM, 200 nM or 300 nM with 3-fold dilutions and injected at a flow rate of 50 μl/min for 3 minutes, followed by dissociation for another 30 minutes at the end of the last injection. HER2 dilutions were analyzed in duplicate. Sensograms were fit globally to a 1:1 Langmuir binding model. All experiments were conducted at 25° C.

[0405] The results are shown in FIG. **12** and FIG. **13**.

[0406] The results in FIG. **12**A show the ka (1/Ms) of monovalent anti-HER2 (v630 and v4182) and exemplary biparatopic anti-HER2 antibody (v5019) for binding to recombinant human HER2 over a range of injected and captured antibody concentrations on the surface of the chip. These results show that ka does not change when for v630, v4182 and v5019 at different antibody capture levels.

[0407] The results in FIG. **12**B show the kd (1/s) of monovalent anti-HER2 (v630 and v4182) and exemplary biparatopic anti-HER2 antibody (v5019) for binding to recombinant human HER2 over a range of injected and captured antibody concentrations on the surface of the chip. These results show that kd decreased only for the exemplary anti-HER2 biparatopic antibody (v5019) at increasing antibody capture levels.

[0408] The results in FIG. **12**C show the K_D (M) of monovalent anti-HER2 (v630 and v4182) and exemplary biparatopic anti-HER2 antibody (v5019) for binding to recombinant human HER2 over a range of injected and captured antibody concentrations on the surface of the chip. These results show that K_D decreased only for the exemplary anti-HER2 biparatopic antibody (v5019) at increasing antibody capture levels. This result correlated to the decreasing kd values shown in FIG. **15**B.

[0409] The results in FIG. **13**A show the kd (1/s) of exemplary biparatopic anti-HER2 antibody (v5019) for binding to recombinant human HER2 over a range of antibody capture levels. These results show kd values are inversely proportional to higher RUs of antibody captured on the surface of the chip (i.e slower off-rates at higher antibody capture levels). The results indicate that exemplary biparatopic anti-HER2 antibody (v5019) is capable of binding HER2 ECD2 and HER2 ECD4 on two separate HER2 molecules (i.e. trans binding) as is evidenced by the reduction in off-rate at higher antibody capture levels. This data is supported by a similar experiment presented in FIG. **47** and discussed in Example 43, where bivalent monospecific anti-HER2 FSA (v506) demonstrated Cis binding (1:1 antibody to HER2) where the kd (1/s) and K_D (M) values remained constant at increasing antibody capture levels as is expected for this molecule.

[0410] The results in FIG. **13**B show the kd (1/s) of monovalent anti-HER2 antibody (v4182) for binding to recombinant human HER2 over a range of antibody capture levels. These results show no change in kd values over the range of different antibody RUs captured on the surface of the chip. These results show that monovalent anti-HER2 antibody (v4182) is binding monovalently 1:1 (cis binding).

[0411] The results in FIG. **13**C show the kd (1/s) of monovalent anti-HER2 antibody (v630) for binding to recombinant human HER2 over a range of antibody capture levels. These results show no change in kd values over the range of different antibody RUs captured on the surface of the chip. These results show that monovalent anti-HER2 antibody (v630) is binding monovalently 1:1 (cis binding). This data is supported by the experiment presented in FIG. **47** and discussed in Example 43X, where the bivalent monospecific anti-HER2 FSA (v506) showed no change in kd (1/s).

[0412] The results in FIG. **12**, and FIG. **13** indicate that exemplary biparatopic anti-HER2 antibody (v5019) is capable of simultaneously binding to two HER2 molecules in trans (antibody to HER2 ratio 1:2). The trans mechanism of binding detected by SPR is consistent with the higher cell surface saturation binding data (Bmax), presented in Example 6, in combination with the internalization data presented in Examples 9 and 10.

Example 13: Effect of Exemplary Biparatopic Anti-HER2 Antibody Incubation on AKT Phosphorylation in BT-474 Cells

[0413] The ability of an exemplary anti-HER2 biparatopic antibody to reduce pAKT signaling in BT-474 cells was tested using the AKT Colorimetric In-Cell ELISA Kit (Thermo Scientific; cat no. 62215) according to the manufacturer's instructions with the following modifications. Cells were seeded at 5×10^3/well and incubated 24 h at 37° C.+5% CO_2. Cells were incubated with 100 nM antibody for with 30 min followed by a 15 min incubation with rhHRG-f31. Cells were washed, fixed, and permeabilized according to the instructions. Secondary antibodies (1:5000; Jackson ImmunoReasearch, HRP-donkey anti-mouse IgG, JIR, Cat#715-036-150, HRP-donkey anti-rabbit IgG, JIR, Cat#711-036-452) were added and the assay processed according to the manufacturer's instructions.

[0414] The results in FIG. **15** show that incubation with exemplary anti-HER2 biparatopic antibody mediated an approximate 1.2-fold reduction in p-Akt levels in the presence of HRGβ1 relative to the human IgG control (CTL). The combination of two anti-HER2 FSAs (v506+v4184) mediated the greatest reduction in p-Akt levels in the presence HRGβ1 that was approximately 1.5-fold less compared to the human IgG control. A modest reduction in p-Akt was detected with the exemplary anti-HER2 biparatopic antibody in the absence of ligand (HRGβ1) compared to the human IgG control antibody.

[0415] These data show that exemplary anti-HER2 biparatopic antibody can block ligand-activated signaling in HER2+ cells.

Example 14: Effect of Biparatopic Anti-HER2 Antibody on Cardiomyocyte Viability

[0416] The effect of exemplary biparatopic anti-HER2 antibodies and ADCs on cardiomyocyte viability was measured in order to obtain a preliminary indication of potentially cardiotoxic effects.

[0417] iCell cardiomyocytes (Cellular Dynamics International, CMC-100-010), that express basal levels of the HER2 receptor, were grown according the manufacturer's instructions and used as target cells to assess cardiomyocyte health following antibody treatment. The assay was performed as follows. Cells were seeded in 96-well plates (15,000 cells/well) and maintained for 48 h. The cell medium was replaced with maintenance media and cells were maintained for 72h. To access the effects of antibody-induced cardiotoxicity, cells were treated for 72 h with 10 and 100 nM of, variants alone or in combinations. To access the effects of anthracycline-induced cardiotoxicity (alone or in combination with the exemplary biparatopic anti-HER2 antibodies), cells were treated with 3 uM (~IC_{20}) of doxorubicin for 1 hr followed by 72 h with 10 and 100 nM of, antibody variants alone or in combinations. Cell viability was assessed by quantitating cellular ATP levels with the CellTiter-Glo® Luminescent Cell Viability Assay (Promega, G7570) and/or Sulphorhodamine (Sigma 230162-5G) as per the manufacturer's instructions.

[0418] The results are shown in FIG. **16**A-C. The results in FIG. **16**A show that incubation of the cardiomyocytes with therapeutically relevant concentrations of exemplary anti-HER2 biparatopic antibody (v5019) and exemplary anti-HER2 biparatopic-ADC (v6363), did not affect cardiomyocyte viability relative to the untreated control ('mock').

[0419] The results in FIG. **16**B show that incubation of the cardiomyocytes with therapeutically relevant concentrations of exemplary anti-HER2 biparatopic antibodies (v5019, v7091 and v10000), and exemplary anti-HER2 biparatopic-ADCs (v6363, v7148 and v10553), had no effect on cardiomyocyte viability relative to the untreated control ('mock'). Based on the results in FIGS. **16**A and **16**B it is expected that exemplary anti-HER2 biparatopic antibodies and exemplary anti-HER2 biparatopic-ADCs should not induce cardiomyopathy, for example through mitochondrial dysfunction, as is reported with other anti-HER2 targeting antibodies (Grazette L. P. et al. Inhibition of ErbB2 Causes Mitochondrial Dysfunction in Cardiomyocytes; Journal of the American College of Cardiology: 2004; 44:11).

[0420] The results in FIG. **16**C show that pretreatment of the cardiomyocytes with doxorubicin followed by incubation with therapeutically relevant concentrations of exemplary anti-HER2 biparatopic antibodies (v5019, v7091 and v10000) and exemplary anti-HER2 biparatopic-ADCs (v6363, v7148 and v10553), had no effect on cardiomyocyte viability relative to the untreated control+doxorubicin ('Mock+Dox'). Based on the results in FIG. **16**C it is expected that exemplary anti-HER2 biparatopic antibodies and exemplary anti-HER2 biparatopic-ADCs should not result in an increased risk of cardiac dysfunction in patients receiving concurrent anthracycline treatment (Seidman A, Hudis C, Pierri M K, et al. Cardiac dysfunction in the trastuzumab clinical trials experience. J Clin Oncol (2002) 20:1215-1221).

[0421] FIGS. **16**A-C show that incubation of cardiomyocytes with the anti-HER2 biparatopic antibodies and ADCs had equivalent effects compared to monospecific anti-HER2 FSA antibody (v506), anti-HER2 FSA combination (v506+v4184) and ADC (v6246) when treated either alone, or in combination with doxorubicin. Based on these results, it is expected that exemplary anti-HER2 biparatopic antibodies and ADCs would not have greater cardiotoxic effects compared to anti-monospecific anti-HER2 FSA, trastuzumab or ADC, T-DM1.

Example 15: Cytotoxicity of Exemplary Biparatopic Anti-HER2-ADCs in HER2+ Cells

[0422] The ability of exemplary biparatopic anti-HER2-ADC antibodies (v6363, v7148 and v10553) to mediate cellular cytotoxicity in HER2+ cells was measured. Human IgG conjugated to DM1 (v6249) was used as a control in some cases. The experiment was carried out in HER2+ breast tumor cell lines JIMT-1, MCF7, MDA-MB-231, the HER2+ ovarian tumor cell line SKOV3, and HER2+ gastric cell line NCI-N87. The cytotoxicity of exemplary biparatopic anti-HER2-ADC antibodies in HER2+ cells was evaluated and compared to the monospecific anti-HER2 FSA-ADC (v6246) and anti-HER2-FSA-ADC+ anti-HER2-FSA controls (v6246+v4184). The method was conducted as described in Example 7 with the following modifications. The anti-HER2 ADCs were incubated with the target SKOV3 and JIMT-1 (FIGS. **17**A and B) cells for 24 h, cells washed, media replaced and cell survival was evaluated after 5 day incubation at 37° C. The anti-HER2 ADCs were incubated with target MCF7 and MDA-MB-231 target cells for 6 h (FIGS. **17**C and D), cells washed media replaced and cell survival was evaluated at 5 days incubation at 37° C. In

FIG. **17**E-G, anti-HER2 ADCs were incubated continuously with target SKOV3, JIMT-1, NCI-N87 cells for 5 days. Cell viability was measured as described in Example 7 using either AlamarBlue™ (FIGS. **17**A-D) or Celltiter-Glo® (FIGS. **17**E-G).

[0423] The results are shown in FIG. **17**A-G and the data is summarized in Tables 15 and 16.

[0424] The results in FIG. **17**A and Table 15 and 16 show that exemplary anti-HER2 biparatopic-ADC (v6363) is more cytotoxic in JIMT-1 compared to the anti-HER2-FSA-ADC (v6246) and the combination of anti-HER2-FSA-ADC+ anti-HER2 FSA (v6246+v4184). The exemplary anti-HER2 biparatopic-ADC had a superior EC_{50} that was approximately 13-fold lower compared to the anti-HER2 FSA-ADC control.

[0425] The results in FIG. **17**B and Table 15 show that exemplary anti-HER2 biparatopic-ADC (v6363) is more cytotoxic in SKOV3 compared to the anti-HER2-FSA-ADC (v6246) and the combination of anti-HER2-FSA-ADC+ anti-HER2 FSA (v6246+v4184). The exemplary anti-HER2 biparatopic-ADC had a superior EC_{50} that was approximately 5-fold lower compared to the anti-HER2 FSA-ADC control.

[0426] The results in FIG. **17**C and Table 15 show that exemplary anti-HER2 biparatopic-ADC (v6363) is more cytotoxic in MCF7 compared to the anti-HER2-FSA-ADC (v6246) and the combination of anti-HER2-FSA-ADC+ anti-HER2 FSA (v6246+v4184). The exemplary anti-HER2 biparatopic-ADC had a superior EC_{50} that was approximately 2-fold lower compared to the anti-HER2 FSA-ADC control.

[0427] The results in FIG. **17**D and Table 15 show that exemplary anti-HER2 biparatopic-ADC (v6363) is more cytotoxic in MDA-MB-231 compared to the anti-HER2-FSA-ADC (v6246) and the combination of anti-HER2-FSA-ADC+ anti-HER2 FSA (v6246+v4184). The exemplary anti-HER2 biparatopic-ADC had a superior EC_{50} that was approximately 2-fold lower compared to the anti-HER2 FSA-ADC control.

TABLE 15

⑦	⑦			
⑦	⑦	⑦	⑦	⑦⑦
v6246	0.9225	5.942	122.0	~1075
v6246 + 4184	3.146	12.68	~24432	136.4
v6363	0.1776	0.4443	58.55	141.0

⑦ indicates text missing or illegible when filed

[0428] The results in FIG. **17**E and Table 16 show that exemplary anti-HER2 biparatopic-ADCs (v6363, v7148 and v10553) are more cytotoxic in SKOV3 ovarian tumor cells compared to the anti-HER2-FSA-ADC (v6246). The exemplary anti-HER2 biparatopic-ADCs had a superior EC_{50} values that were approximately 2 to 7-fold lower compared to the anti-HER2 FSA-ADC control.

[0429] The results in FIG. **17**F and Table 16 show that exemplary anti-HER2 biparatopic-ADCs (v6363, v7148 and v10553) are more cytotoxic in JIMT-1 breast tumor cells compared to the anti-HER2-FSA-ADC (v6246). The exemplary anti-HER2 biparatopic-ADCs had a superior EC_{50} values were approximately 6 to 9-fold lower compared to the anti-HER2 FSA-ADC control.

[0430] The results in FIG. **17**G and Table 16 show that exemplary anti-HER2 biparatopic-ADCs (v6363, v7148 and v10553) are cytotoxic in NCI-N87 gastric tumor cells. The exemplary anti-HER2 biparatopic-ADCs had has approximately equivalent EC_{50} values compared to the anti-HER2 FSA-ADC control.

TABLE 16

Antibody	EC_{50} (nM)		
variant	SKOV3	JIMT-1	NCI-N87
v6246	0.22	3.52	1.04
v6363	0.03	0.56	1.33
v7148	0.06	0.56	2.74
v10553	0.09	0.39	1.69

These results show that exemplary anti-HER2 biparatopic-ADCs (v6363, v7148 and v10553) are more cytotoxic compared to anti-HER-FSA-ADC control in HER2 3+, 2+, and 1+ breast tumor cells. These results also show that exemplary anti-HER2 biparatopic-ADCs (v6363, v7148 and v10553) are cytotoxic in HER2 2/3+ gastric tumor cells. These results are consistent with the internalization results presented in Example 9.

Example 16: Effect of a Biparatopic Anti-HER2 Antibody in a Human Ovarian Cancer Cell Xenograft Model

[0431] The established human ovarian cancer cell derived xenograft model SKOV3 was used to assess the anti-tumor efficacy of an exemplary biparatopic anti-HER2 antibody.

[0432] Female athymic nude mice were inoculated with the tumor via the insertion of a 1 mm^3 tumor fragment subcutaneously. Tumors were monitored until they reached an average volume of 220 mm^3; animals were then randomized into 3 treatment groups: IgG control, anti-HER2 FSA (v506), and biparatopic anti-HER2 antibody (v5019).

[0433] Fifteen animals were included in each group. Dosing for each group is as follows:

[0434] A) IgG control was dosed intravenously with a loading dose of 30 mg/kg on study day 1 then with maintenance doses of 20 mg/kg twice per week to study day 39.

[0435] B) Anti-HER2 FSA (v506) was dosed intravenously with a loading dose of 15 mg/kg on study day 1 then with maintenance doses of 10 mg/kg twice per week to study day 18. On days 22 through 39, 5 mg/kg anti-HER2 FSA was dosed intravenously twice per week. Anti-HER2 FSA (v4184) was dosed simultaneously at 5 mg/kg intraperitoneally twice per week.

[0436] C) Biparatopic anti-HER2 antibody was dosed intravenously with a loading dose of 15 mg/kg on study day 1 then with maintenance doses of 10 mg/kg twice per week to study day 39.

[0437] Tumor volume was measured twice weekly over the course of the study, number of responders and median survival was assessed at day 22. The results are shown in FIG. **18** and Table 17.

[0438] The biparatopic anti-HER2 and anti-HER2 FSA demonstrated superior tumor growth inhibition compared to IgG control. The biparatopic anti-HER2 antibody induced superior tumor growth inhibition compared to anti-HER2 FSA combination (FIG. **18**A). The biparatopic anti-HER2 antibody was associated with an increase in the number of

responding tumors compared to anti-HER2 FSA v506 at day 22 (11 and 5, respectively)(Table 17). The exemplary biparatopic anti-HER2 antibody and anti-HER2 FSA demonstrated superior survival compared to IgG control. The biparatopic anti-HER2 antibody had a superior median survival (61 days) compared to anti-HER2 FSA (36 days) (FIG. **18**B and Table 17). On study day 22 a second anti-HER2 FSA (v4184) was added in combination to the anti-HER2 FSA (v506). The combination of two anti-HER2 FSAs induced a further tumour growth inhibition compared to anti-HER2 FSA (v506) alone.

TABLE 17

n = 15, Day 22	IgG	v506	v5019
Mean TV (mm3) (% change from Baseline)	1908 (+766%)	1291 (+486%)	697 (+217%)
% TGI	0	32	63
Responders (TV <50% of control)	0/15	5/15	11/15
Median Survival (days)	22	36	61

Example 17: Effect of a Biparatopic Anti-HER2 Antibody Drug Conjugate (ADC) in a Human Ovarian Cancer Cell Line Xenograft Model

[0439] The established human ovarian cancer cell derived xenograft model SKOV3 was used to assess the anti-tumor efficacy of an exemplary biparatopic anti-HER2 antibody conjugated to DM1 (v6363).

[0440] Female athymic nude mice were inoculated with the tumor via the insertion of a 1 mm^3 tumor fragment subcutaneously. Tumors were monitored until they reached an average volume of 220 mm^3; animals were then randomized into 3 treatment groups: IgG control, anti-HER2 FSA-ADC, and a biparatopic anti-HER2-ADC.

[0441] Fifteen animals were included in each group. Dosing for each group is as follows:

[0442] A) IgG control was dosed intravenously with a loading dose of 30 mg/kg on study day 1 then with maintenance doses of 20 mg/kg twice per week to study day 39.

[0443] B) Anti-HER2 FSA-ADC (v6246) was dosed intravenously with a loading dose of 10 mg/kg on study day 1 then with a maintenance dose of 5 mg/kg on day 15 and 29.

[0444] C) Biparatopic anti-HER2 antibody-ADC (v6363) was dosed intravenously with a loading dose of 10 mg/kg on study day 1 then with a maintenance dose of 5 mg/kg on day 15 and 29.

[0445] Tumor volume was measured throughout the study, and the number of responders and median survival was assessed at day 22. The results are shown in FIG. **19**. A summary of the results is shown in Table 18.

[0446] The biparatopic anti-HER2-ADC and anti-HER2 FSA-ADC inhibited tumor growth better than IgG control (FIG. **19**A and Table 18). The biparatopic anti-HER2-ADC inhibited tumor growth to a greater degree than did the anti-HER2 FSA-ADC. The biparatopic anti-HER2-ADC group was associated with an increase in the number of responding tumors compared to anti-HER2 FSA-ADC (11 and 9, respectively). The biparatopic anti-HER2-ADC and anti-HER2 FSA-ADC groups demonstrated superior survival compared to IgG control (FIG. **19**B and Table 18). The biparatopic anti-HER2 antibody group demonstrated median survival of 61 days compared to the anti-HER2 FSA-ADC which had a median survival of 36 days (FIG. **19**B and Table 18).

TABLE 18

n = 15, Day 22	IgG	v6246	v6363
Mean TV (mm3) (% change from Baseline)	1908 (+766%)	873 (+297%)	632 (+187%)
% TGI	0	54%	67%
Responders (TV <50% of control)	0/15	9/15	11/15
Median survival (days)	22	36	61

Example 18: Effect of a Biparatopic Anti-HER2 Antibody Drug Conjugate (ADC) in a Human Primary Cell Xenograft Model (HBCx-13b)

[0447] The trastuzumab resistant patient derived xenograft model from human breast cancer, HBCx-13B, was used to assess the anti-tumor efficacy of an exemplary biparatopic anti-HER2 antibody conjugated to DM1.

[0448] Female athymic nude mice were inoculated with the tumor via the insertion of a 20 mm^3 tumor fragment subcutaneously. Tumors were monitored until they reached an average volume of 100 mm^3; animals were then randomized into 3 treatment groups: anti-HER2 FSA (v506), anti-HER2 FSA-ADC (v6246), and the biparatopic anti-HER2-ADC (v6363). Seven animals were included in each group. Dosing for each group was as follows:

[0449] A) Anti-HER2 FSA was dosed intravenously with a loading dose of 15 mg/kg on study day 1 and maintenance doses of 10 mg/kg administered on study days 4, 8, 11, 15, 18, 22, and 25.

[0450] B) Anti-HER2 FSA-ADC was dosed intravenously with a loading dose of 10 mg/kg on study day 1 then with a maintenance dose of 5 mg/kg on day 22.

[0451] C) Biparatopic anti-HER2 antibody-ADC was dosed intravenously with a loading dose of 10 mg/kg on study day 1 then with a maintenance dose of 5 mg/kg on day 22.

[0452] Tumor volume was measured throughout the study, and mean tumor volume, complete response, and zero residual disease parameters were assessed at Day 50. The results are shown in FIG. **20**. A summary of the results is shown in Table 19.

[0453] The biparatopic anti-HER2-ADC and anti-HER2 FSA-ADC demonstrated greater tumor growth inhibition compared to an anti-HER2 FSA (v506). The biparatopic anti-HER2-ADC inhibited tumor growth better than the anti-HER2 FSA-ADC. The biparatopic anti-HER2-ADC group as compared to the anti-HER2 FSA-ADC group was associated with an increase in the number of tumors showing complete responses (more than a 10% decrease below baseline), 7 and 4 respectively, and showing zero residual disease, 5 and 2 respectively.

TABLE 19

n = 7, Day 50	v506	v6246	v6363
Mean TV (mm3) (% change from Baseline)	1149 (+1018%)	262 (+153%)	26 (−75%)

TABLE 19-continued

n = 7, Day 50	v506	v6246	v6363
% TGI	0%	77%	98%
Complete response (>10% baseline regression)	0	4/7	7/7
Zero residual disease (TV <20 mm3)	0	2/7	5/7

Example 19: Effect of a Biparatopic Anti-HER2 Antibody Drug Conjugate (ADC) in a Human Primary Cell Xenograft Model (T226)

[0454] The patient derived trastuzumab resistant xenograft model from human breast cancer, T226, was used to assess the anti-tumor efficacy of an exemplary biparatopic anti-HER2-ADC.

[0455] Female athymic nude mice were inoculated with the tumor via the insertion of a 20 mm^3 tumor fragment subcutaneously. Tumors were monitored until they reached an average volume of 100 mm^3; animals were then randomized into 4 treatment groups: IgG control (n=15), anti-HER2 FSA (v506; n=15), anti-HER2 FSA-ADC (v6246; n=16), and the biparatopic anti-HER2-ADC conjugate (v6363; n=16). Dosing for each group was as follows:

[0456] A) IgG control was dosed intravenously with a loading dose of 15 mg/kg on study day 1 and maintenance doses of 10 mg/kg administered on study days 4, 8, 11, 15, 18, 22, and 25

[0457] B) Anti-HER2 FSA was dosed intravenously with a loading dose of 15 mg/kg on study day 1 and maintenance doses of 10 mg/kg administered on study days 4, 8, 11, 15, 18, 22, and 25

[0458] C) Anti-HER2 FSA-ADC was dosed intravenously with 5 mg/kg on study days 1 and 15

[0459] D) Biparatopic anti-HER2-ADC conjugate was dosed intravenously with 5 mg/kg on study days 1 and 15.

[0460] Tumor volume was measured throughout the course of the study, and mean tumor volume and complete response parameters were assessed at day 31. The results are shown in FIG. **21**. A summary of the results is shown in Table 20.

[0461] The biparatopic anti-HER2-ADC and anti-HER2 FSA-ADC demonstrated better tumor growth inhibition compared to the anti-HER2 FSA (v506) and IgG control. The exemplary biparatopic anti-HER2-ADC induced equivalent tumor growth inhibition and complete baseline regression compared to anti-HER2 FSA-ADC (FIG. **21** and Table 20) in this model.

TABLE 20

Day 31	IgG (n = 13)	v506 (n = 13)	v6246 (n = 16)	v6363 (n = 16)
Mean TV (mm3) (% change from Baseline)	1797 (+1728%)	1611 (+1573)	422 (+332%)	572 (+483%)
% TGI (vs. hIgG)	0%	11%	77%	68%
Complete response (>10% baseline regression)	0/13	0/14	1/16	1/16

Example 20: Effect of a Biparatopic Anti-HER2 Antibody Drug Conjugate (ADC) in a Human Primary Cell Xenograft Model (HBCx-5)

[0462] The patient derived trastuzumab resistant xenograft model from human breast cancer, HBCx-5 (invasive ductal carcinoma, luminal B), was used to assess the anti-tumor efficacy of an exemplary biparatopic anti-HER2-ADC.

[0463] Female athymic nude mice were inoculated with the tumor via the insertion of a 20 mm^3 tumor fragment subcutaneously. Tumors were monitored until they reached an average volume of 100 mm^3; animals were then randomized into 4 treatment groups: IgG control (n=15), anti-HER2 FSA (v506; n=15), anti-HER2 FSA-ADC (v6246; n=16), and the biparatopic anti-HER2-ADC (v6363; n=16). Dosing for each group was as follows:

[0464] A) IgG control was dosed intravenously with a loading dose of 15 mg/kg on study day 1 and maintenance doses of 10 mg/kg administered on study days 4, 8, 11, 15, 18, 22, and 25

[0465] B) Anti-HER2 FSA was dosed intravenously with a loading dose of 15 mg/kg on study day 1 and maintenance doses of 10 mg/kg administered on study days 4, 8, 11, 15, 18, 22, and 25

[0466] C) Anti-HER2 FSA-ADC was dosed intravenously with 10 mg/kg on study days 1 and 15, 22, 29, 36

[0467] D) Biparatopic anti-HER2-ADC was dosed intravenously with 10 mg/kg on study days 1 and 15, 22, 29, 36.

[0468] Tumor volume was measured throughout the course of the study, and the mean tumor volume, T/C ratio, number of responders, complete response, and zero residual disease parameters were assessed at day 43. The results are shown in FIG. **22**. A summary of the results is shown in Table 21.

[0469] The biparatopic anti-HER2-ADC and anti-HER2 FSA-ADC demonstrated better tumor growth inhibition compared to an anti-HER2 FSA (v506) and IgG control. The exemplary biparatopic anti-HER2-ADC induced equivalent tumor growth inhibition and had an increased number of responders compared to anti-HER2 FSA-ADC (FIG. **22** and Table 21) in the trastuzumab resistant HBCx-5 human breast cancer xenograft model.

TABLE 21

Day 43	IgG (n = 4)	Herceptin (n = 5)	T-DM1 (n = 7)	6363 (n = 7)
Mean TV (mm3) (% change from Baseline)	922 (+693%)	815 (+598%)	193 (+65%)	241 (+106%)
T/C (IgG) ratio	1	0.88	0.21	0.26
Responders (TV<50% of control)	0/4	1/5	6/7	7/7
Complete response (>10% baseline regression)	0/4	0/5	1/7	0/7
Zero residual disease (TV <20 mm3)	0/4	0/5	0/7	0/7

Example 21: Effect of a Biparatopic Anti-HER2 Antibody Drug Conjugate (ADC) to Anti-HER2 Treatment Resistant Tumors in a Human Cell Line Xenograft Model (SKOV3)

[0470] The established human ovarian cancer cell derived xenograft model SKOV3, described in Example 17, was

used to assess the anti-tumor efficacy of an exemplary biparatopic anti-HER2-ADC in anti-HER2 treatment resistant tumors.

[0471] The methods were followed as described in Example 17 with the following modifications. A cohort of animals was dosed with an anti-HER2 antibody intravenously with 15 mg/kg on study day 1 and with 10 mg/kg on day 4, 8, 15; however, this treatment failed to demonstrate an efficacious response by day 15 in this model. This treatment group was then converted to treatment with the exemplary biparatopic anti-HER2 antibody drug conjugate (v6363) and was dosed with 5 mg/kg and on study day 19 and 27 and 15 mg/kg on study day 34, 41 and 48.

[0472] Tumor volume was measured twice weekly throughout the course of the experiment.

[0473] The results are shown in FIG. **23** and indicate that the group treated with exemplary biparatopic anti-HER2-ADC (v6363) showed tumor regression to a mean tumor volume less than the initial mean starting volume of 220 mm^3.

Example 22: Effect of a Biparatopic Anti-HER2 Antibody Drug Conjugate (ADC) on Anti-HER2 Treatment Resistant Tumors in Human Primary Cell Xenograft Model (HBCx-13b)

[0474] The trastuzumab resistant patient derived xenograft model from human breast cancer, HBCx-13B, was used to assess the anti-tumor efficacy of an exemplary biparatopic anti-HER2 antibody conjugated to DM1.

[0475] The methods were followed as described in Example 18 with the following modifications. A cohort of animals was dosed with a bi-specific anti-ErbB family targeting antibody intravenously with 15 mg/kg on study day 1 and with 10 mg/kg on day 4, 8, 15, 18, 22, and 25; however, this treatment failed to demonstrate an efficacious response. This treatment group was then converted to treatment with the exemplary biparatopic anti-HER2 antibody drug conjugate (v6363) and was dosed with 10 mg/kg on days 31, 52 and with 5 mg/kg on day 45. Tumor volume was measured throughout the duration of the study.

[0476] The results are shown in FIG. **24**. These results show that the exemplary biparatopic anti-HER2-ADC (v6363) prevented tumour progression. From the first dose to day 57 the tumour volume of the v6363 treated group increased by less than 2% while in the same interval the v506 treated group grew by more than 110%.

Example 23: Analysis of Fucose Content of an Exemplary Biparatopic Anti-HER2 Antibody

[0477] Glycopeptide analysis was performed to quantify the fucose content of the N-linked glycan of the exemplary biparatopic anti-HER2 antibodies (v5019, v7091 and v10000).

[0478] The glycopeptide analysis was performed as follows. Antibody samples were reduced with 10 mM DTT at 56° C. 1 h and alkylated with 55 mM iodoacetamide at RT 1 h and digested in-solution with trypsin in 50 mM ammonium bicarbonate overnight at 37° C. Tryptic digests were analyzed by nanoLC-MS/MS on a QTof-Ultima. The NCBI database was searched with Mascot to identify protein sequences. MaxEnt3 (MassLynx) was used to deconvolute the glycopeptide ions and to quantify the different glycoforms.

[0479] A summary of the glycopeptide analysis results is in Table 22. The N-linked glycans of exemplary biparatopic anti-HER2 antibodies (v5019, v7091 and v10000) are, approximately 90% fucosylated (10% N-linked glycans without fucose). The N-linked glycans of monospecific anti-HER2 FSA (v506) are, approximately 96% fucosylated (4% N-linked glycans without fucose) and Herceptin® is approximately 87% fucosylated (4% N-linked glycans without fucose).

TABLE 22

Fc N-linked Glycopeptide Analysis

Antibody Variant	Average % of Glycopeptides Observed With Fucose	Average % of Glycopeptides Observed Without Fucose	n
v506	96.4	3.6	5
Herceptin ®	86.5	13.4	4
v5019	90.5	9.4	6
v7091	89.9	26.9	3
v10000	89.2	10.7	5

[0480] These results show that biparatopic anti-HER2 antibodies (with a heterodimeric Fc), expressed transiently in CHO cells, have approximately 3% higher fucose content in the N-glycan compared to commercial Herceptin®. The homodimeric anti-HER2 FSA (v506), expressed transiently in CHO cells, has the highest fucose content of approximately 96%.

Example 24: Thermal Stability of an Exemplary Biparatopic Anti-HER2 Antibody

[0481] Thermal stability of exemplary biparatopic anti-HER2 antibodies (v5019, v7091 and v10000) and ADCs (v6363, v7148 and v10533) was measured by DSC as described below.

[0482] DSC was performed in the MicroCal™ VP-Capillary DSC (GE Healthcare) using a purified protein sample (anti-HER2 biparatopic antibodies and anti-HER2 biparatopic-ADCs) adjusted to about 0.3 mg/ml in PBS. The sample was scanned from 20 to 100° C. at a 60° C./hr rate, with low feedback, 8 sec filter, 5 min preTstat, and 70 psi nitrogen pressure. The resulting thermogram was analyzed using Origin 7 software.

[0483] The thermal stability results of exemplary biparatopic anti-HER2 antibodies (v5019, v7091 and v10000) are shown in FIG. **25**A-C. FIG. **25**A shows the thermogram for v5019; the Fc and chain A Fab of each have a T_m of 75° Celsius and the chain B scFv of 5019 has a T_m of 69° Celsius. FIG. **25**B shows the thermogram for v10000; the Fc CH3 domain has a T_m 82° Celsius, Fab chain A has T_m of 76.5° Celsius and the chain B scFv has a T_m of 69.5° Celsius. FIG. **25**C shows the thermogram for v7091; the Fc CH3 domain has a T_m 82° Celsius, Fab chain A has T_m of 76.7° Celsius and the chain B scFv has a T_m of 69.5° Celsius.

[0484] The thermal stability results of exemplary biparatopic anti-HER2 ADCs (v6363, v7148 and v10533) are shown in FIG. **26**A-C. FIG. **26**A shows the thermogram for v6363; the Fc has a T_m of 75° Celsius and the chain A Fab and Fc CH3 domain have a T_m of 75° Celsius. The chain B scFv of 6363 has a T_m of 69° Celsius. FIG. **26**B shows the thermogram for v10553; the Fc CH3 domain has a T_m of 83° Celsius, the chain A Fab has a T_m of 75.7° Celsius and the chain B scFv has a T_m of 66.2° Celsius. FIG. **26**C shows the

thermogram for v7148; the Fc CH3 domain has a T_m of 82.6° Celsius, the chain A Fab has a T_m of 74.8° Celsius and the chain B scFv has a T_m of 66.6° Celsius.

[0485] The exemplary biparatopic antibodies and ADCs have thermal stability comparable to wildtype IgG.

Example 25: Ability of an Exemplary Biparatopic Anti-HER2 Antibody to Elicit ADCC of Breast Tumor Cells Expressing Varying Levels of HER2

[0486] The ability of exemplary biparatopic antibody (v5019) to elicit dose-dependent ADCC of HER2 positive 3+, 2+, and 0/1+ HER2 expressing (triple-negative) breast cancer cell lines was examined. The ADCC experiments were performed as described in Example 11 with the exception that NK effector cell to target cell ratio remained constant at 5:1.

[0487] The ADCC results are shown in FIG. **27** and Table 23. The results in FIG. **27**A-C show that exemplary biparatopic antibody (v5019) elicits approximately 1.2 to 1.3-fold greater maximum cell lysis of HER2 positive 3+, 2+ and 0/1+ HER2 expressing breast cancer cells compared to Herceptin®. The results also show that v5019 (90% N-glycans with fucose) more effectively mediates ADCC of HER2 positive 3+, 2+ and 0/1+ HER2 expressing breast cancer despite having approximately a 4% higher fucose content in the N-glycan (resulting in lower binding affinity to CD16 on NK cells) compared to Herceptin® (86% N-glycans with fucose; Example 23). The higher target cell killing elicited by v5019 is presumably due to increased tumor cell decoration as described in Example 6.

TABLE 23

ADCC of HER2 3+, 2+ and 0/1+ HER2 expressing breast cancer cells

	SKBr3 HER2 3+		JIMT-1 HER2 2+		MDA-MB-231 HER2 0/1+	
Treatment	Max % Target Cell Lysis	EC_{50} (nM)	Max % Target Cell Lysis	EC_{50} (nM)	Max % Target Cell Lysis	EC_{50} (nM)
v5019	30	~0.9	60	0.001	53	0.9
Herceptin ®	23	~0.9	51	0.002	44	0.9

[0488] The ADCC results in FIG. **27**D show that exemplary biparatopic antibodies (v7091 and v10000) elicit similar maximal cell lysis compared to Herceptin® in the basal HER2 expressing WI-38 cell line. The ADCC results support the cell binding data (Example 6), showing that a threshold for increased binding and ADCC occurs when the HER2 receptor levels are greater than 10,000 HER2/cell. Based on this data it would be expected that the exemplary biparatopic anti-HER2 antibodies would have increased cell surface binding and ADCC of HER2 3+, 2+ and 1+ tumor cells but would not have increase cell surface binding and ADCC of non-tumor cells that express basal levels of the HER2 receptor at approximately 10,000 receptors or less.

Example 26: Effect of Antibody Afucosylation on ADCC

[0489] The ability of afucosylated exemplary biparatopic antibodies (v5019-afuco, 10000-afuco) to elicit dose-dependent ADCC of HER2 positive 2/3+, 2+ and 0/1+ HER2 expressing (triple-negative) breast cancer cell lines, was examined. ADCC experiments were performed as described in Example 11, in SKOV3 cells, MDA-MB-231 cells and ZR75-1 cells with the exception that a constant NK effector cell or PBMC effector to target (E:T) cell ratio of 5:1 was used. Afucosylated exemplary biparatopic antibodies were produced transiently in CHO cells as described in Example 1, using the transiently expressed RMD enzyme as described in von Horsten et al. 2010 Glycobiology 20:1607-1618. The fucose content of v5019-afuco and v10000-afuco were measured as described in Example 23 and determined to be less <2% fucosylated (data not shown). Data using NK effector cells is shown in FIG. **28**A-B, while data using PBMCs is shown in FIG. **28**C.

[0490] FIG. **28**A, FIG. **28**B and Table 24 show that afucosylated v5019 (v5019-afuco) elicits ADCC of HER 2/3+ and 0/1+ HER2 expressing breast cancer cells with approximately 1.5 to 1.7-fold higher maximum cell lysis than Herceptin®.

TABLE 24

ADCC of HER2 2/3+ and basal HER2 expressing (triple-negative) breast cancer cells

	SKOV3 HER2 2+/3+		MDA-MD-231 HER2 0/1+	
Treatment	Max % Target Cell Lysis	EC_{50} (nM)	Max % Target Cell Lysis	EC_{50} (nM)
v5019-afucosylated	24	~0.6	58	~0.6
Herceptin ®	14	~0.6	40	~0.3

[0491] The results in FIG. **28**C and Table 25 show that v10000 elicits ADCC of HER2 2+ ZR-75-1 breast cancer cells with approximately 1.3-fold greater maximal cell lysis than Herceptin®, and v10000-afuco elicits approximately 1.5-fold greater maximal cell lysis than Herceptin®.

TABLE 25

ADCC of HER2 2/3+ breast cancer cells

	ZR-751 HER2 2+	
Treatment	Max % Target Cell Lysis	EC_{50} (nM)
v10000	28	~0.06
v10000-afucosylated	32	~0.7
Herceptin ®	21	~0.5

[0492] The ADCC results show that the exemplary afucosylated biparatopic antibodies (v5019-afuco, v10000-afuco) elicit approximately 15-25% greater maximum cell

lysis compared to the fucosylated antibodies (v5019 Example 25, v10000) when Herceptin® is used as a benchmark. These results show that reducing the fucose content of the Fc N-glycan results in increased maximal cell lysis by ADCC.

Example 27: Ability of Exemplary Biparatopic Anti-HER2 Antibody to Inhibit Growth of HER2 3+ Breast Cancer Cells in the Presence of Exogenous Growth-Stimulatory Ligands (EGF and HRG)

[0493] The ability of 5019 to inhibit growth of HER2 3+ breast cancer cells in the presence of exogenous growth-stimulatory ligands (EGF and HRG) was examined.

[0494] Test antibodies and exogenous ligand (10 ng/mL HRG or 50 ng/mL EGF) were added to the target BT-474 HER2 3+ cells in triplicate and incubated for 5 days at 37° C. Cell viability was measured using AlamarBlue™ (37° C. for 2 hr), absorbance read at 530/580 nm. Data was normalised to untreated control and analysis was performed using GraphPad Prism.

[0495] The results are shown in FIG. **29** and Table 26. The results show that exemplary biparatopic antibody v5019 inhibits the growth of HER2 3+ breast cancer cells in the absence of growth stimulatory ligand (70% inhibition), as well as in the presence of EGF (40% inhibition) or HRG (~10% inhibition). The anti-HER2 monospecific FSA (v506) does not block EGF or HRG induced tumor cell growth via other erbB receptors EGFR and HER3. v5019 is superior to v506 in inhibiting HER2 and ligand-dependent dimerization and growth via other companion erbB receptors.

TABLE 26

Growth Inhibition of HER2 3+ Cancer Cells

	% Survival		
Treatment	Antibody only	+EGF	+HRG
Mock	100	122	110
v506	41	114	129
v5019	31	56	92

[0496] These results show that exemplary biparatopic antibody is capable of reducing ligand-dependent growth of HER2+ cells, presumably due binding of the anti-ECD2 chain A Fab arm and subsequent blocking of ligand stimulated receptor homo- and heterodimerization, and erbB signaling.

Example 28: Effect of a Biparatopic Anti HER2 Antibody in a Trastuzumab-Resistant and Chemotherapy Resistant HER2 3+ Patient-Derived (PDX) Metastatic Breast Cancer Xenograft Model of Invasive Ductal Breast Carcinoma

[0497] The HER2 3+ (ER-PR negative) patient derived xenograft model from invasive ductal human breast cancer, HBCx-13B, was used to assess the anti-tumor efficacy of an exemplary biparatopic anti-HER2 antibody, v7187. v7187 is an afucosylated version of v5019. The model is resistant to single agent trastuzumab, the combination of trastuzumab and pertuzumab (see example 31), capecitabine, docetaxel, and adriamycin/cyclophosphamide.

[0498] Female athymic nude mice were inoculated subcutaneously with a 20 mm^3 tumor fragment. Tumors were then monitored until reaching an average volume of 140 mm3. Animals were then randomized into 2 treatment groups: vehicle control and v7187 with eight animals in each group. IV Dosing was as follows. Vehicle control was dosed intravenously with 5 ml/kg of formulation buffer twice per week to study day 43. v7187 was dosed intravenously with 10 mg/kg twice per week to study day 43. Tumor volume was measured throughout the study, and other parameters assessed at day 43 as shown in Table 27.

[0499] The results are shown in FIG. **30** and Table 27. The results show that tumors treated with vehicle control showed continual progression and exceeded 1600 mm^3 by study day 43. Mice treated with v7187 showed significantly greater tumor growth inhibition (T/C−0.44) with a mean tumor volume of 740 mm^3 on day 43. v7187 induced responses in 5/8 tumors with a single tumor showing complete regression with zero residual disease on study day 43. Animals treated with v7187 had a superior response rate with 5/8 tumors responding to therapy compared to 0/8 mice treated with vehicle control. In addition, treatment with v7187 significantly delayed tumor progression compared to vehicle control with doubling times of 19 and 11 days respectively.

TABLE 27

Tumour Response		Vehicle	V7087
Day 43	Mean TV (mm3) (% Change from Baseline)	1683 (+1079%)	740 (+422%)
	T/C ratio	1	0.44
	Responders (TV < 50% of control)	0/8	5/8
	PR (>10% baseline regression)	0/8	1/8
	ZRD (TV < 20 mm3)	0/8	1/8
Time to progression	Doubling time (days)	11	19

[0500] These data show that the exemplary anti-HER2 biparatopic (v7187) is efficacious in a Trastuzumab+Pertuzumab resistant HER2 3+ metastatic breast cancer tumor xenograft model. V7187 treatment has a high response rate and can significantly impair tumor progression of standard of care treatment resistant HER2 3+ breast cancers.

Example 29: Assessment of Biparatopic Anti-HER2 ADC Binding to HER2+ Tumor Cell Lines

[0501] The ability of exemplary biparatopic anti-HER2 ADCs to bind and saturate HER2 positive 3+, 2+, breast and ovarian tumor cell lines was analyzed by FACS as described in Example 6.

[0502] The data is shown in FIG. **31**. FIG. **31**A shows v6363 binding to SKOV3 tumor cell lines with approximately a 2.0-fold greater Bmax (MFI) than T-DM1 (v6246) at saturating concentrations. FIG. **31**B shows v6363 binds to JIMT-1 tumor cell lines with approximately a 1.6-fold greater Bmax (MFI) than T-DM1 (v6246) at saturating concentrations. These data show that v6363 (ADC) has similar tumor cell binding properties of increased cell surface binding compared to the parent unconjugated v5019 antibody (Example 6). Conjugation of v5019 with SMCC-DM1 (v6363) does not alter the antigen-binding properties of the antibody.

[0503] The FACS binding assay was repeated to include direct comparison to the exemplary biparatopic antibodies

(v5019, v7091 and v10000) and ADCs (v6363, v7148 and v10553). The data is shown in FIG. **31**C and FIG. **31**D. The exemplary biparatopic anti-HER2 ADCs (v6363, v7148 and v10553) have equivalent cell surface saturation (Bmax) compared to the unlabeled biparatopic antibodies (v5019, v7091 and v10000).

[0504] These data show that conjugation of exemplary biparatopic antibodies (v5019, v7091 and v10000) with SMCC-DM1 does not alter the binding properties. The exemplary anti-HER2 biparatopic anti-HER2 ADCs (v6363, v7148 and v10553) have approximately 1.5-fold (or greater) increased cell surface binding compared to a monospecific anti-HER2 ADC (v6246, T-DM1).

Example 30: Dose-Dependent Tumour Growth Inhibition of an Exemplary Anti-HER2 Biparatopic-ADC in a HER2 3+ (ER-PR Negative) Patient Derived Xenograft Model

[0505] The HER2 3+ (ER-PR negative) patient derived xenograft model from invasive ductal human breast cancer, HBCx-13B, was used to assess the anti-tumor efficacy of an exemplary biparatopic anti-HER2 ADC, v6363. The model is resistant to single agent trastuzumab, the combination of trastuzumab and pertuzumab (see example 31), capecitabine, docetaxel, and adriamycin/cyclophosphamide.

[0506] Female athymic nude mice were inoculated with the tumor via the subcutaneous insertion of a 20 mm^3 tumor fragment. Tumors were monitored until they reached an average volume of 160 mm^3; animals were then randomized into 5 treatment groups: non-specific human IgG control, and 4 escalating doses of v6363. 8-10 animals were included in each group. Dosing for each group was as follows. IgG control was dosed intravenously with 10 mg/kg twice per week to study day 29. v6363 was dosed intravenously with 0.3, 1, 3, or 10 mg/kg on study days 1, 15, and 29. Tumor volume was assessed throughout the study and parameters assessed as indicated in Table 29.

[0507] The results are shown in FIG. **32** and Table 28. These results show that the exemplary anti-HER2 biparatopic ADC (v6363) mediated dose-dependent tumor growth inhibition in the Trastuzumab-resistant HBCx-13b PDX model (FIG. **32**A). In addition, v6363 improved overall survival in a dose-dependent manner, with median survival time of more than 63 days for 3 mg/kg and 10 mg/kg doses compared to 43 days for IgG control (FIG. **32**B and Table 28). The 3 mg/kg dose was associated with an increased response rate (5/10) compared to control (0/8). All mice treated with v6363 at 10 mg/kg dose not only responded to therapy (9/9) but also showed prevention of tumor progression. Moreover, the majority of tumors had objective partial responses (7/9) and, at the end of the study, many had zero residual disease (6/9). v6363 was well tolerated at all doses, no adverse events were observed and no body weight loss was observed.

TABLE 28

Tumour Response		IgG	6363 0.3 mg/kg	6363 1 mg/kg	6363 3 mg/kg	6363 10 mg/kg
Day 43	Mean TV (mm3) (% change from Baseline)	1963 (+1119%)	1916 (+1073%)	1613 (+895%)	1268 (+682%)	84 (−49%)
	T/C (IgG) ratio	1	0.97	0.82	0.64	0.04
	Responders (TV < 50% of control)	0/8	0/10	2/10	5/10	9/9
	PR (>10% baseline regression)	0/8	0/10	0/10	0/10	7/9
	ZRD (TV < 20 mm3)	0/8	0/10	0/10	0/10	6/9
Time to progression	Tumor doubling time (days)	9	9	14	17	52
Survival Response	Median Survival (Days)	43	41	50	>63	>63
Body Weight	% Change from Baseline	+10%	+10%	+9%	+5%	+0%

[0508] These data show that the exemplary anti-HER2 biparatopic ADC (v6363) is efficacious in a Trastuzumab+ Pertuzumab resistant HER2 3+ metastatic breast cancer tumor xenograft model. v6363 treatment is associated with a high response rate, significantly impairs tumor progression, and prolongs survival in a standard of care resistant HER2 3+ breast cancers.

Example 31: Biparatopic Anti-HER2-ADC Compared to Standard of Care Combinations in the Trastuzumab Resistant PDX HBCx-13b

[0509] The efficacy of v6363 in a HER2 3+, ER-PR negative Trastuzumab resistant patient-derived breast cancer xenograft model (HBCx-13b), was evaluated and compared to to the combination of: Herceptin™+Perjeta™; and Herceptin™+Docetaxel.

[0510] Female athymic nude mice were inoculated with the tumor via the subcutaneous insertion of a 20 mm3 tumor fragment. Tumors were monitored until they reached an average volume of 100 mm3; animals were then randomized into 4 treatment groups (8-10 animals/group): non-specific human IgG control, Herceptin™+Docetaxel, Herceptin™+Perjeta™, and v6363. Dosing for each group was as follow. IgG control was dosed intravenously with 10 mg/kg twice per week to study day 29. Herceptin™+Docetaxel combination Herceptin™ was dosed intravenously with 10 mg/kg IV twice weekly to study day 29 and Docetaxel was dosed intraperitoneally with 20 mg/kg on study day 1 and 22. Herceptin™+Perjeta™ combination Herceptin was dosed intravenously with 5 mg/kg twice per week to study day 29 and Perjeta™ was dosed intravenously with 5 mg/kg twice per week to study day 29. The dosing of Herceptin™ and Perjeta™ was concurrent. v6363 was dosed intravenously with 10 mg/kg on study day 1, 15, and 29.

[0511] The results are shown in FIG. **33** and Table 29. FIG. **33**A shows tumor volume over time, and FIG. **33**B shows a survival plot. These results show that the combination of Herceptin™+Perjeta™ did not produce any tumor growth inhibition compared to control IgG and exceeded 1800 mm^3 on day 39. The combination of Herceptin™+Docetaxel did not significantly reduce tumor growth but did prolong median survival to 53 days compared to 43 days for IgG control. v6363 produced significant tumor growth inhibition (T/C−0.04), where, all tumors responded to therapy and 7/10 tumors experienced complete regressions (zero residual disease). v6363 significantly prolonged survival compared to both combination therapies. Body weights across cohorts were not significantly affected by treatments.

TABLE 29

Tumour Response		IgG	HerceptinTM + PerjetaTM	HerceptinTM + Docetaxel	v6363 10 mg/kg
Day 39	Mean TV (mm3) (% change from Baseline)	1809 (+1023%)	1975 (+1085%)	1328 (+714%)	76 (−54%)
	T/C (IgG) ratio	1.0	1.10	0.73	0.04
	Responders (TV < 50% of control)	0/8	0/8	1/10	9/9
	PR (>10% baseline regression)	0/8	0/8	0/10	8/9
	ZRD (TV < 20 mm3)	0/8	0/8	0/10	6/9
Survival Response	Median Survival (days)	43	39	53	>63
Body Weight	% Change from Baseline	+10%	+7%	+3%	−2%

[0512] These results show that exemplary anti-HER2 biparatopic ADC (v6363) is superior to standard of care combinations with respect to all parameters tested in this xenograft model.

Example 32: Efficacy of a Biparatopic Anti-HER2-ADC in HER2+ Trastuzumab-Resistant Breast Cancer Cell Derived Tumour Xenograft Model

[0513] The efficacy of v6363 in a HER2 3+ Trastuzumab resistant breast cancer cell-derived (JIMT-1, HER2 2+) xenograft model was evaluated (Tanner et al. 2004. Molecular Cancer Therapeutics 3: 1585-1592).

[0514] Female RAG2 mice were inoculated with the tumor subcutaneously. Tumors were monitored until they reached an average volume of 115 mm^3; animals were then randomized into 2 treatment groups: Trastuzumab (n=10) and v6363. Dosing for each group was as follows. Trastuzumab was dosed intravenously with 15 mg/kg on study day 1 and 10 mg/kg twice per week to study day 26. v6363 was dosed intravenously with 5 mg/kg on study days 1 and 15 and with 10 mg/kg on day 23 and 30 and 9 mg/kg on day 37 and 44.

[0515] The results are shown in FIG. **34** and Table 30. These results show that v6363 significantly inhibited tumor growth (T/C−0.74) compared to Trastuzumab on study day 36. v6363 and Trastuzumab treatment did not significantly change body weight. v6363 serum exposure was 17.9 μg/ml 7 days after the first 10 mg/kg dose.

TABLE 30

Tumour Response		Trastuzumab	6363
Day 36	Mean TV (mm3) (% change from Baseline)	718 (+541)	532 (+335%)
	T/C (Tras) ratio	1	0.74
	Responders (TV < 50% of control)	1/10	2/13
	PR (>10% baseline regression)	0/10	0/13
	ZRD (TV < 20 mm3)	0/10	0/13
Body Weight	% Change from Baseline	+5.8%	+3.1%
Drug Exposure (day 7)	Mean Serum Concentration (ug/ml)	187.2	17.9

[0516] These results show that exemplary anti-HER2 biparatopic ADC (v6363) is efficacious in a Trastuzumab-resistant breast cancer and has a potential utility in treating breast cancers that are resistant to current standards of care.

Example 33: FcγR Binding to Heterodimeric Fc of Anti-HER2 Biparatopic Antibodies and Anti-HER2 Biparatopic-ADCs

[0517] The binding of anti-HER2 biparatopic antibody (v5019, v7019 v10000) and ADC (v6363, v7148 and v10553) having a heterodimeric Fc, to human FcγRs was assessed and compared to anti-HER2 FSA (v506) and ADC (v6246) having a homodimeric Fc.

[0518] Affinity of FcγR to antibody Fc region was measured by SPR using a ProteOn XPR36 (BIO-RAD). HER2 was immobilized (3000 RU) on CMS chip by standard amine coupling. Antibodies were antigen captured on the HER2 surface. Purified FcγR was injected various concentration (20-30 μl/min) for 2 minutes, followed by 4 minute dissociation. Sensograms were fit globally to a 1:1 Langmuir binding model. Experiments were conducted at 25° C.

[0519] The results are shown in Table 31. The exemplary heterodimeric anti-HER2 biparatopic antibodies and ADCs bound to CD16aF, CD16aV158, CD32aH, CD32aR131, CD32bY163 and CD64A with comparable affinities. Conjugation of the antibodies with SMCC-DM1 does not negatively affect FcγR binding. The heterodimeric anti-HER2 biparatopic antibodies have approximately 1.3 to 2-fold higher affinity to CD16aF, CD32aR131, CD32aH compared to homodimeric anti-HER2 FSA (v506) and ADC (v6246). These results show that the heterodimeric anti-HER2 biparatopic antibodies and ADCs bind different polymorphic forms of FcγRs on immune effector cells with similar or greater affinity than a WT homodimeric IgG1.

TABLE 31

Human Fc7R Binding by SPR												
	10 uM CD16a v158		10 uM CD16aF		10 uM CD32aR131		10 uM CD32aH		10 uM CD32b Y163		100 nM CD64A	
Variant	KD Ave	SD	KD Ave	SD	KD Ave	SD	KD Ave	SD	KD Ave	SD	KD Ave	SD
v506	1.5E−07	2E−08	7.1E−07	1.E−08	7.6E−07	1.E−07	6.3E−07	2E−08	2.4E−06	1.E−07	8.64E−10	4.33E−10
v6246	1.6E−07	2E−08	7.0E−07	9.E−09	7.4E−07	7.E−08	6.3E−07	2E−08	2.1E−06	7.E−08	1.08E−09	5.13E−10
v10000	1.2E−07	1E−08	4.8E−07	2.E−08	5.1E−07	9.E−08	4.6E−07	2E−08	1.5E−06	7.E−08	8.41E−10	4.74E−10
v10553	1.2E−07	2E−08	4.9E−07	2.E−07	3.5E−07	1.E−07	3.6E−07	4E−09	1.2E−06	7E−08	4.95E−10	1.41E−10
v7091	1.2E−07	1E−08	5.1E−07	2.E−08	5.6E−07	9.E−08	5.0E−07	3E−08	1.7E−06	8E−08	9.68E−10	5.05E−10
v7148	1.2E−07	2E−08	5.4E−07	2.E−07	3.7E−07	1.E−07	4.2E−07	1E−08	1.5E−06	1.E−07	5.77E−10	2.02E−10
v5019	1.3E−07	1E−08	5.2E−07	1.E−08	5.6E−07	6.E−08	4.7E−07	2E−08	1.6E−06	2.E−07	8.44E−10	4.88E−10
v6363	1.2E−07	2E−08	4.5E−07	1.E−07	3.5E−07	1.E−07	3.4E−07	1E−08	1.2E−06	5.E−08	4.58E−10	1.13E−10

Example 34: Efficacy of Exemplary Anti-HER2 Biparatopic Antibodies In Vivo in a Trastuzumab Sensitive Ovarian Cancer Cell Derived Tumour Xenograft Model

[0520] The established human ovarian cancer cell derived xenograft model SKOV3, described in Example 17, was used to assess the anti-tumor efficacy of the exemplary biparatopic anti-HER2 antibodies, v5019, v7091 and v10000.

[0521] Female athymic nude mice were inoculated with a tumor suspension of 325,000 cells in HBSS subcutaneously on the left flank. Tumors were monitored until they reached an average volume of 190 mm^3 and enrolled in a randomized and staggered fashion into 4 treatment groups: non-specific human IgG control, v5019, v7091, and v10000. Dosing for each group was as follows. Non-specific human IgG was dosed intravenously with 10 mg/kg starting on study day 1 twice per week to study day 26. V5019, v7091, and v10000 were dosed intravenously with 3 mg/kg starting on study day 1 twice per week to study day 26. Tumor volume was measured throughout the study, and the parameters listed in Table 32 were measured at day 29.

[0522] The data are presented in FIG. **35**A (tumor growth), FIG. **35**B (survival plot) and Table 32 and show that treatment with v5019, v7091 and v10000 resulted in comparable tumor growth inhibition (T/C: 0.53-0.71), number of responding tumors, time to progression, and survival on study day 29 compared to IgG control. The serum exposure of v5019, v7091, and v10000 was similar (31-41 microg/ml) on study day 7.

TABLE 32

Tumour Response		IgG (n = 8)	v5019 (n = 11)	V7091 (n = 11)	V10000 (n = 11)
Day 29	Mean TV (mm3) (% change from Baseline)	1903 (+899%)	1001 (+416%)	1354 (+618%)	1114 (+503%)
	T/C (Tras) ratio	1	0.53	0.71	0.58
	Responders (TV < 50% of control)	1/8	5/11	4/11	6/11
	PR (>10% baseline regression)	0/8	1/11	0/11	0/11
	ZRD (TV < 20 mm3)	0/8	0/11	0/11	0/11
Time to progression	Tumor doubling time (days)	12	15	16	15
Survival	Median survival (days)	29	Na	37	41
Drug Exposure (day 7)	Mean Serum Concentration (ug/ml)	na	31.2	41.0	31.2

[0523] These results show that the exemplary anti-HER2 biparatopic antibodies, v5019, v7091, and v10000) have potential utility in treating moderately Trastuzumab sensitive HER2 overexpressing ovarian cancers.

Example 35: Exemplary Biparatopic Anti-Her2 Antibodies Dose-Dependently Inhibit Tumour Growth in the Trastuzumab-Sensitive Ovarian Cancer Cell Derived Tumour Xenograft

[0524] The established human ovarian cancer cell derived xenograft model SKOV3, described in Example 17, was used to assess the dose-dependent efficacy of an exemplary biparatopic anti-HER2 antibody, v10000.

[0525] Female athymic nude mice were inoculated with a tumor suspension of 325,000 cells in HBSS subcutaneously on the left flank. Tumors were monitored until they reached an average volume of 190 mm^3 and enrolled in a randomized and staggered fashion into 6 treatment groups: non-specific human IgG control and 5 escalating doses of v10000. 9-13 animals were included in each group. Dosing for each group was as follows. IgG control was dosed intravenously with 10 mg/kg twice per week to study day 26. V10000 was dosed intravenously with 0.1, 0.3, 1, 3, or 10 mg/kg twice per week.

[0526] The data are presented in FIG. **36** and Table 33 and show that treatment with v10000 dose dependently induces tumor growth inhibition (T/C: 0.28-0.73) compared to control IgG. In addition, v10000 was dose-dependently associated with responding tumors (7/9 at 10 mg/kg and 3/11 at 0.1 mg/kg) increased time to progression (24 days at 10 mg/kg and 12 days at 0.1 mg/kg) on study day 29. The serum exposure of v10000 on day 7 was dose dependent and increased from 0.46 microg/ml with a 0.1 mg/kg dose to 79.3 microg/ml with a 10 mg/kg dose.

TABLE 33

Tumor Response		IgG (n = 8)	V10000, 10 mg/kg (n = 9)	V10000, 3 mg/kg (n = 11)	V10000, 1 mg/kg (n = 11)	V10000, 0.3 mg/kg (n = 13)	V10000, 0.1 mg/kg (n = 11)
Day 29	Mean TV (mm3) (% change from Baseline)	1903 (+899%)	543 (+281%)	1114 (+503%)	1534 (+688%)	1535 (+694%)	1385 (+643%)
	T/C ratio	1	0.28	0.58	0.81	0.81	0.73
	Responders (TV < 50% of control)	1/8	7/9	6/11	2/11	3/13	3/11
	PR (>10% baseline regression)	0/8	1/9	0/11	0/11	0/13	0/11
	ZRD (TV < 20 mm3)	0/8	0/9	0/11	0/11	0/13	0/11
Time to Progression	Tumor doubling time (days)	12	24	15	14	12	12
Drug Exposure (Day 7)	Mean Serum Concentration (ug/ml)	na	79.3	31.2	4.7	1.5	0.46

[0527] These results show that the exemplary anti-HER2 biparatopic antibody, v10000, inhibits tumor progression in a dose-dependent manner.

Example 36: Ability of Anti-HER2 Biparatopic Antibody and Anti-HER2 Biparatopic-ADC to Inhibit Growth of Cell Lines Expressing HER2, and EGFR and/or HER3 at the 3+, 2+ or 1+ Levels

[0528] The following experiment was performed to measure the ability of an exemplary biparatopic anti-HER2 antibody (v10000) and corresponding biparatopic anti-HER2 ADC (v10553) to inhibit growth of a selection of breast, colorectal, gastric, lung, skin, ovarian, renal, pancreatic, head and neck, uterine and bladder tumor cell lines that express HER2, and EGFR and/or HER3 at the 3+, 2+, 1+ or 0+ level as defined by IHC.

[0529] The experiment was conducted as follows. The optimal seeding density for each cell line was uniquely determined to identify a seeding density that yielded approximately 60-90% confluency after the 72 hr duration of the assay. Each cell line was seeded at the optimal seeding density, in the appropriate growth medium per cell line, in a 96-well plate and incubated for 24° C. at 36° C. and 5% CO_2. Antibodies were added at three concentrations (v10000 at 300, 30 and 0.3 nM; v10553 at 300, 1, 0.1 nM), along with the positive and vehicle controls. The positive control chemococktail drug combination of 5-FU (5-fluorouracil), paclitaxel, cisplatin, etoposide (25 microM), the vehicle control consisted of PBS. The antibody treatments and controls were incubated with the cells for 72 h in a cell culture incubator at 36° C. and 5% CO_2. The plates were centrifuged at 1200 RPM for 10 min and culture medium completely removed by aspiration. RPMI SFM medium (200 microL) and MTS (20 microL) was added to each well and incubated at 36° C. and 5% CO_2 for 3 h. Optical density was read at 490 nM and percent growth inhibition was determined relative to the vehicle control.

[0530] The results are shown in FIG. **37** and a summary of all test results are shown in FIG. **38**. FIG. **37**A shows the growth inhibition results of v10000. These results show that v10000 can inhibit growth of breast, colorectal, gastric, lung, skin, ovarian, renal, pancreatic, head and neck, uterine, and endometrial tumor cell lines that express HER2 and coexpress EGFR and/or HER3 at the 3+, 2+, 1+ or 0+ level. The activity of v10000 and v10553 at 300 nM is summarized in FIG. **38**, where '+' indicates cell lines that showed a

reduction in cell viability at 300 nM that was >5% of the vehicle control, and '-' indicates ≤5% viability of the vehicle control.

[0531] FIG. **37**B shows the growth inhibition results of v10553. These results show that v10553 can inhibit growth of breast, colorectal, gastric, lung, skin, ovarian, renal, pancreatic, head and neck, uterine and bladder tumor cell lines that express HER2 and coexpress EGFR and/or HER3 at the 3+, 2+, 1+ or 0+ level (see also FIG. **38**). The results plotted in FIG. **37**B are defined by cell lines that showed a minimum of dose-dependent growth inhibition at 300 and 1 nM, and where the growth inhibition at 1 nM is equal or greater than 5% (FIG. **37**B).

[0532] These results show that exemplary biparatopic antibody v10000 and ADC v10553 can inhibit growth of tumor cells originating from breast, colorectal, gastric, lung, skin, ovarian, renal, pancreatic, head and neck, uterine and bladder histologies that express HER2 at the 3+, 2/3+, 2+, 1+ and 0/1+ levels and that coexpress EGFR and/or HER3 at the 2+, 1+ levels.

Example 37: Ability of Anti-HER2 Biparatopic Antibodies to Mediate ADCC of HER2 2+, 1+ and 0/1+ Cancer Cells

[0533] The following experiment was conducted to determine the ability of anti-HER2 biparatopic antibodies to mediate ADCC of tumor cells that express HER2 at the 2+, 1+ and/or 0/1+ levels and that coexpress EGFR and/or HER3 at the 2+ or 1+ level. The anti-HER2 biparatopic antibodies tested were 5019, 10000, and 10154 (an afucosylated version of v10000), with Herceptin™ and v506 as controls.

[0534] The ADCC experiment was conducted as described in Example 11 and Example 25 with E/T: 5:1 with NK-92 effector cells (FIG. **39**), and as described in Example 26 with E/T 30:1 with PBMC effector cells.

[0535] The results are shown in FIG. **39** (NK-92 effector cells) and FIG. **40** (PBMC effector cells). FIG. **39**A shows the ADCC results of the HER2 2+ head and neck tumor cell line (hypopharyngeal carcinoma), FaDu, where the anti-HER2 biparatopic elicits approximately 15% maximal cell lysis. FIG. **39**C shows the ADCC results of the HER2 1+BxPC3 pancreatic tumor cell line, and FIG. **39**D the results of the HER2 2+ MiaPaca2 pancreatic tumor cell line. FIG. **39**B shows the ADCC results of the HER2 0/1+A549 NSCLC (non-small cell lung cancer) tumor cell line. In the BxPC3, MiaPaca2 and A549 tumor cell lines, v10000 mediated approximately 5% maximal tumor cell lysis.

[0536] FIG. **40** shows the ADCC results in A549, NCI-N87, and HCT-116 cells, where PBMCs were used as the effector cells. FIG. **40**A shows the ADCC results of the HER2 0/1+A549 NSCLC tumor cell line, where v10000 elicited ~28% maximum cell lysis and this was comparable to Herceptin™ that has equivalent level of fucose content in the N-linked glycan. The exemplary 100% afucosylated (0% fucose) biparatopic v10154 shows an increase in maximal cell lysis (40% maximum cell lysis) and increased potency compared to v10000 and Herceptin that have approximately 88% fucose in the N-linked glycan.

[0537] FIG. **40**B shows the ADCC results of the HER2 3+ gastric tumor cell line, NCI-N87. FIG. **40**B shows that exemplary biparatopic v5019 (approximately 88% fucosylated) mediates approximately 23% maximal cell lysis and has a lower EC50 compared to Trastuzumab v506 (approximately 98% fucosylated).

[0538] FIG. **40**C shows the ADCC results of the HER2 1+ HCT-116 colorectal tumor cell line. FIG. **40**C shows that exemplary biparatopic v5019 (approximately 88% fucosylated) mediates approximately 25% maximal cell lysis and is more potent compared to Trastuzumab v506 (approximately 98% fucosylated).

[0539] These results show that exemplary anti-HER2 biparatopic antibodies can elicit ADCC of HER2 01/+, 2+ and 3+ tumor cells that originate from head and neck, gastric, NSCLC, and pancreatic tumor histologies. ADCC in the presence of NK-92 cells as the effector cells had an apparent HER2 2+ receptor level requirement (i.e. 2+ or greater) to show higher (>5%) percentage of maximum cell lysis. However, when PBMC cells were used as effector cells higher levels of maximum cell lysis were achieved (>5% and up to 28% or 40%; v10000 and v10154, respectively) and were independent of HER2 receptor density as ADCC >5% was seen at the 0/1+, 1+ and 3+ HER2 receptor density levels.

Example 38: HER2 Binding Affinity and Kinetics as Measured by SPR

[0540] As indicated in Example 1, anti-HER2 biparatopic antibodies having different antigen-binding moiety formats were constructed, as described in Table 1. The formats included scFv-scFv format (v6717), Fab-Fab format (v6902 and v6903), along with Fab-scFv format (v5019, v7091, and v10000). The following experiment was conducted to compare HER2 binding affinity and kinetics of these exemplary anti-HER2 biparatopic antibody formats.

[0541] Affinity and binding kinetics to murine HER2 ECD (Sino Biological 50714-M08H) was measured by single cycle kinetics with the T200 SPR system from Biacore (GE Healthcare). Between 2000-4000 RU of anti-human Fc was immobilized on a CMS chip using standard amine coupling. 5019 was captured on the anti-human Fc surface at 50 RU. Recombinant HER2 ECD (1.8-120 nM) was injected at 50 µl/min for 3 minutes, followed by a 30 minute dissociation after the last injection. HER2 dilutions were analyzed in duplicate. Sensorgrams were fit globally to a 1:1 Langmuir binding model. All experiments were conducted at room temperature, 25° C.

[0542] The results in Table 34 show that Fab-scFv biparatopic antibodies (v5019 and v7091), Fab-Fab variants (v6902 and v6903) and the scFv-scFv variant (v6717) have comparable binding affinity (1-4 nM). The Fab-scFv variant v10000 had higher binding affinity (lower KD) of approximately 0.6 nM. The monspecific anti-HER2 ECD4 antibody (v506) and anti-HER2 ECD2 antibody (v4184) were included in the assay as controls. These results indicate that the molecular formats including v6717, v6902, v6903, v5019 and/or v7091 have equivalent binding affinities, and thus differences in function between these antibodies may be considered to result from differences in format.

TABLE 34

Anti-body Variant	AVERAGE Ka (1/Ms)	AVERAGE Kd (1/s)	AVERAGE KD (M)	STD DEV Ka (1/Ms)	STD DEV Kd (1/s)	STD DEV KD (M)
v506	7.34E+04	4.08E−05	5.56E−10	1.13.E+03	3.04E−06	3.28E−11
v4184	3.61E+04	5.46E−04	1.56E−08	7.78.E+03	2.80E−05	4.12E−09
v5019	6.01E+04	7.77E−05	1.29E−09	1.30.E+03	8.56E−07	4.24E−11
v7091	5.17E+04	1.19E−04	2.31E−09	2.70.E+03	1.49E−05	4.09E−10
v10000	6.44E+04	3.69E−05	5.79E−10	6.18.E+03	6.72.E−06	1.42.E−10
v6902	6.83E+04	1.72E−04	2.72E−09	1.93E+04	4.49E−05	1.43E−09
v6903	7.10E+04	1.71E−04	2.75E−09	3.60E+04	3.96E−06	1.34E−09
v6717	1.50E4-05	5.33E−04	4.45E−09	1.28E+05	2.54E−04	2.11E−09

Example 39: Effect of Anti-HER2 Biparatopic Antibody Format on Binding to HER2+ Tumor Cells

[0543] The following experiment was conducted to compare the whole cell binding properties (Bmax and apparent K_D) of exemplary anti-HER2 ECD2×ECD4 biparatopic antibodies that have different molecular formats (e.g. v6717, scFv-scFv IgG1; v6903 and v6902 Fab-Fab IgG1; v5019, v7091 and v10000 Fab-scFv IgG1).

[0544] The experiment was conducted as described in Example 6. The results are shown in FIG. **41** and Tables 35-38. FIG. **41**A and Table 35 shows the FACS binding results of the exemplary biparatopic antibodies to the BT474 HER2 3+ breast tumor cell line. The results show that all anti-HER2 antibodies have a higher Bmax (1.5 to 1.7-fold greater) when compared to the monospecific bivalent anti-HER2 antibody v506. The Fab-scFv (v5019, v7091 and v10000) and the Fab-Fab (v6903) formats had approximately a 1.7-fold increased Bmax and the scFv-scFv format (v6717) had a 1.5-fold increased Bmax compared to v506. An equimolar combination of FSAs v506 and v4184 resulted in a 1.7-fold increase in Bmax. The apparent K_D of the exemplary anti-HER2 biparatopic antibodies was approximately 2 to 3-fold higher compared to the monospecific v506.

TABLE 35

FACS binding BT-474

Antibody Variant	K_D (nM)	Bmax
v506	9.0	23536
v10000	16	39665
v506 + v4184	16	40320
v5019	21	39727
v7091	22	36718
v6717	30	36392
v6903	31	40321

[0545] FIG. **41**B and Table 36 shows the FACS binding results to the JIMT-1 HER2 2+ breast tumor cell line. The results show that all anti-HER2 antibodies have a higher Bmax (1.5 to 1.8-fold greater) when compared to the monospecific bivalent anti-HER2 antibody v506. The Fab-scFv (v7091 and v10000) and the Fab-Fab (v6903) formats had approximately a 1.7-fold increased Bmax, the scFv-scFv format (v6717) had a 1.5-fold increased Bmax and the Fab-scFv (v5019) and FSA combination (v506+v4184) had a 1.8-fold increased Bmax compared to v506. The apparent K_D of the exemplary anti-HER2 biparatopic Fab-scFv antibodies was approximately 2 to 4-fold higher compared to the monospecific v506; whereas the K_D of the Fab-Fab (v6903) and scFv-scFv (v6717) were approximately 8-fold higher compared to v506.

TABLE 36

FACS Binding JIMT-1

Antibody Variant	K_D (nM)	Bmax
v506	3.5	2574
v10000	7.6	4435
v506 + v4184	8.0	4617
v5019	12	4690
v7091	14	4456
v6717	26	3769
v6903	28	4452

[0546] FIG. **41**C and Table 37 shows the FACS binding results of the exemplary biparatopic antibodies to the HER2 1+ MCF7 breast tumor cell line. The results show that anti-HER2 antibody v10000 and FSA combination (v506+v4184) have a 1.6-fold higher Bmax compared to the monospecific bivalent anti-HER2 antibody v506. The Fab-scFv (v5019, v7091) had approximately a 1.4-fold; the scFv-scFv format (v6717) a 1.3-fold, and the Fab-Fab format (v6903) had a 1.2-fold increased Bmax compared to v506. The apparent K_D of the exemplary anti-HER2 biparatopic Fab-scFv, Fab-Fab (v6903) and FSA combination (v506+v4184) was approximately 2 to 3-fold lower compared to v506; whereas the K_D of the scFv-scFv (v6717) was approximately 3-fold higher compared to v506.

TABLE 37

FACS Binding MCF7

Antibody Variant	K_D (nM)	Bmax
v506 + v4184	4.5	1410
v7091	6.1	1216
v5019	6.3	1201
v10000	6.8	1381
v6903	7.1	1105
v506	12	889
v6717	32	1167

[0547] FIG. **41**D and Table 38 shows the FACS binding results of the exemplary biparatopic antibodies to the HER2 0/1+ MDA-MD-231 breast tumor cell line. The results show that exemplary biparatopic anti-HER2 antibodies had approximately 1.3 to 1.4-fold increased Bmax compared to the monospecific bivalent anti-HER2 antibody v506. The FSA combination (v506+v4184) had a 1.7-fold increased Bmax The apparent K_D of the exemplary anti-HER2 biparatopic Fab-scFv antibodies (v5019, v7091, v10000) and FSA combination (v506+v4184) had an approximate equivalent KD compared to v506; whereas Fab-Fab (v6903) and scFv-scFv (v6717) was approximately 4 and 16-fold higher K_D respectively, compared to v506.

TABLE 38

FACS Binding MDA-MB-231

Antibody Variant	K_D (nM)	Bmax
v506	4.8	395
v10000	5.6	558
v506 + v4184	7.3	662
v7091	7.9	525
v5019	8.7	548
v6903	17	534
v6717	77	524

[0548] The tumor cell binding results show that anti-HER2 biparatopic antibodies with different molecular formats have an increased Bmax on HER2 3+, 2+, 1+ and 0/1+ tumor cells compared to a bivalent monospecific anti-HER2 antibody. Of the different anti-HER2 biparatopic antibodies, the scFv-scFv format had the lowest Bmax gain relative to v506 on HER2 3+, 2+, 1+ and 0/1+ tumor cells These results also show that scFv-scFv and Fab-Fab formats have the greatest increase in K_D on HER2 3+, 2+, 1+ and 0/1+ tumor cells compared monospecific v506 (3 to 16-fold increase) and the biparatopic Fab-scFv formats (approximately 2-fold or greater). The increase in K_D is an indication of a reduction in avid binding and suggests that different biparatopic formats have unique mechanisms of binding to HER2 on the cell surface.

Example 40: Effect of Anti-HER2 Biparatopic Antibody Format on Internalization in HER2+ Cells

[0549] The following experiment was conducted to compare the ability of exemplary anti-HER2 ECD2×ECD4 biparatopic antibodies that have different molecular formats (e.g. v6717, scFv-scFv IgG1; v6903 and v6902 Fab-Fab IgG1; v5019, v7091 and v10000 Fab-scFv IgG1) to internalize in HER2+ cells expressing HER2 at varying levels.

[0550] The experiment was conducted as detailed in Example 9. The results are shown in FIG. **42** and Tables 39-41. FIG. **42**A and Table 39 show the internalization results in HER2 3+BT-474. These results show that the Fab-scFv format (v10000) and the FSA combination (v506+v4184) have 2.2-fold greater quantities of intracellular antibody, compared to the monospecific anti-HER2 v506. The scFv-scFv format (v6717) had 1.9-fold greater; the Fab-scFv formats (v5019 and v7091) had 1.5 to 1.7-fold greater; and the Fab-Fab formats (v6902 and v6903) had 1.2 to 1.3-fold greater quantities of intracellular antibody accumulation compared to v506.

TABLE 39

Internalization BT-474

Antibody Variant	Surface 4° C.	Surface37° C.	Internal 37° C.
v506	2156	1590	3453
v6902	2407	2077	4035
v6903	2717	986	4573
v7091	2759	2227	5111
v5019	2867	2675	5710
v6717	2006	1212	6498
v10000	3355	2851	7528
v506 + v4184	3998	2326	7569

[0551] FIG. **42**B and Table 40 show the internalization results in HER2 2+ JIMT-1. These results show that the Fab-scFv format (v10000) and the FSA combination (v506+v4184) have respectively 1.8 and 1.9-fold greater quantities of intracellular antibody, compared to the monospecific anti-HER2 v506. The scFv-scFv (v6717) and the Fab-scFv formats (v5019) have 1.4-fold greater; and the Fab-scFv (v7091) and Fab-Fab formats (v6902 and v6903) had 1.2-fold greater quantities of intracellular antibody accumulation compared to v506.

TABLE 40

Internalization JIMT-1

Antibody Variant	Surface 4° C.	Surface 37° C.	Internal 37° C.
v506	337	−7.1	759
v6902	389	152	926
v7091	426	102	935
v6903	392	130	945
v5019	437	5.2	1035
v6717	247	31	1082
v10000	474	103	1375
v506 + v4184	583	89	1449

[0552] FIG. **42**C and Table 41 show the internalization results in HER2 1+ MCF7. These results show that the scFv-scFv format and Fab-scFv formats have 3.0 and 2.8-fold greater quantities of intracellular antibody, compared to the monospecific anti-HER2 v506. The Fab-scFv format (v10000) and the FSA combination (v506+v4184) have approximately 2.0-fold; the Fab-scFv (v7091) and Fab-Fab (v6903) formats have 1.8-fold greater quantities of intracellular antibody accumulation compared to v506.

TABLE 41

Internalization MCF7

Antibody Variant	Surface 4° C.	Surface 37° C.	Internal 37° C.
v506	48	10	48
v7091	77	27	87
v6903	81	35	89
v10000	78	20	96
v506 + v4184	87	19	103
v5019	81	17	134
v6717	48	31	145

[0553] These results show that anti-HER2 biparatopic antibodies with different molecular formats have unique degrees of internalization in HER2 3+, 2+ and 1+ tumor cells that varies with respect to the structure and format of the antigen-binding domains. In general, the monospecific FSA combination of v506 and v4184, the Fab-scFv (v10000, v7091 and v5019) and the scFv-scFv (v6717) biparatopic formats had the higher internalization values in the HER2 3+, 2+ and 1+ tumor cells. Whereas, the Fab-Fab biparatopic formats (v6902 and v6903) had the lowest internalization values in the HER2 3+, 2+ and 1+ tumor cells. These data suggest that the molecular format and geometric spacing of the antigen-binding domains has an influence on the ability of the biparatopic antibodies to cross-link HER2 receptors, and subsequently to internalize in HER2+ tumor cells. The Fab-Fab biparatopic format, having the greatest distance between the two antigen-binding domains, resulted in the lowest degree of internalization, whereas the Fab-scFv and scFv-scFv formats, having shorter distances between the antigen-binding domains, had greater internalization in HER2+ cells. This is consistent with the correlation of potency and shorter linker length as described in Jost et al 2013, Structure 21, 1979-1991).

Example 41: Effect of Anti-HER2 Biparatopic Antibody Format on ADCC in HER2+ Cells

[0554] The following experiment was conducted to compare the ability of exemplary anti-HER2 ECD2×ECD4

biparatopic antibodies that have different molecular formats (e.g. v6717, scFv-scFv IgG1; v6903 and v6902 Fab-Fab IgG1; v5019, v7091 and v10000 Fab-scFv IgG1) to mediate ADCC in HER2+ cells expressing HER2 at varying levels.

[0555] Prior to performing the ADCC assay, glycopeptide analysis was performed on the antibody samples to quantify the fucose content in the N-linked glycopeptide. The method was followed as described in Example 23. The results are shown in Table 42; the data shows that exemplary biparatopic variants v5019, v6717, v6903 have equivalent fucose content in the N-linked glycan (91-93%). Antibody samples with equivalent levels of fucose in the N-glycan were selected for the ADCC assay to normalize for fucose content in the interpretation of the ADCC assay results.

TABLE 42

LC-MS Tryptic peptide analysis

Variant	Percentage of Glycopeptides Observed WITH Fucose	Percentage of Glycopeptides Observed WITHOUT Fucose
v6903	90.7	9.3
v6717	92.8	7.2
v5019	91.3	8.7

[0556] The ADCC experiment was conducted as described in Example 11 with E/T: 5:1 with NK-92 effector cells. The ADCC results are shown in FIG. **43** and Tables 43-45. FIG. **43**A and Table 43 show the ADCC results in HER2 2+ JIMT-1 breast tumor cells. These data show that v5019, v6717 and v6903 elicit similar levels of maximum cell lysis and that the scFv-scFv format (v6717) is less potent compared to v5019 and v6903 when HER2 2+ tumor cells are targets.

TABLE 43

JIMT-1 ADCC

Antibody variant	EC50 (nM)	% Max Cell Lysis
v6903	~0.03	48
v5019	~0.16	47
v6717	~0.72	51

[0557] FIG. **43**B and Table 44 show the ADCC results in HER2 1+ MCF7 breast tumor cells. These data show that v5019 and v6717 have slightly higher maximum cell lysis (27-30%) compared to v6903 (24%). These data also show that v6717 is the least potent, followed by v6903 and v5019, which have lower EC50 values.

TABLE 44

MCF7 ADCC

Antibody variant	EC_{50} (nM)	% Max Cell Lysis
v5019	~0.69	27
v6717	109	30
v6903	0.94	24

[0558] FIG. **43**C and Table 45 show the ADCC results in HER2 0/1+ MDA-MB-231 breast tumor cells. These data show that v5019 shows slightly higher maximum cell lysis (77%) compared to v6903 (62%) and v6717 (63%). These data also show that v6717 is the least potent, followed by v6903 and v5019, which have lower EC_{50} values.

TABLE 45

MDA-MB-231 ADCC

Antibody variant	EC_{50} (nM)	% Max Cell Lysis (top only)
v5019	0.20	71
v6717	10	63
v6903	0.79	62

[0559] These data show that exemplary anti-HER2 ECD2×ECD4 biparatopic antibodies elicit similar levels of maximum cell lysis by ADCC in HER2 2+ and 1+ tumor cells. Despite similarities in maximal cell lysis, these data also show that the different molecular formats have unique ADCC potencies. The scFv-scFv was the least potent (greatest EC_{50} values) in the HER2 2+ and HER2 1+. Differential potencies among the three formats was seen in the ADCC data targeting HER2 1+ cells, where the EC50 values for v6717>v6903>v5019. These data are consistent with the observations presented in Example 40 (FACS binding), where an increase in K_D (reduced affinity) was seen with the Fab-Fab and scFv-scFv formats.

Example 42: Effect of Anti-HER2 Biparatopic Antibody Format on Growth of HER2+ Tumor Cells

[0560] The following experiment was conducted to compare the effect of anti-HER2 biparatopic antibody format on growth of HER2 3+, 2+ and 1+ tumor cells, either basal growth or ligand-stimulated. Basal growth was measured as described in Example 15, while ligand-stimulated growth was measured as described in Example 27. In both types of experiments, growth was measured as % survival with respect to control treatment.

[0561] FIG. **44** and Table 46 show the effect of exemplary anti-HER2 ECD2×ECD4 biparatopic antibodies on growth of HER2 3+ breast cancer cells (BT-474) in the presence of exogenous growth-stimulatory ligands (EGF and HRG). In the absence of EGF or HRG, the anti-HER2 biparatopic antibodies were able to inhibit growth of BT-474 cells, where % survival of each treatment group ranked as follows: v6903<v506+v4184<506<v7091<v5019<v10000<v6717. In the presence of HRG, growth inhibition relative to the mock control was achieved only with the FSA combination of v506+v4184. In the presence of EGF, growth inhibition relative to the mock control was achieved, where % survival of each treatment group ranked as follows: v6903<v506+v4184<7091<v10000<5019.

TABLE 46

Treatment	% Survival		
	Antibody only	+HRG	+EGF
Mock	100	143	131
v6717	113	126	129
v10000	70	118	78
v5019	67	133	81
v7091	61	119	61
v506	53	141	118
v506 + v4184	43	89	45
v6903	32	120	39

[0562] FIG. **45** shows the dose-dependent effect of the anti-HER2 biparatopic antibody formats on growth inhibition of the SKBr3 HER2 3+ cell line. The data is consistent with the results presented in FIG. **44**, where the rank order

potency/efficacy of the biparatopic formats is as follows Fab-Fab>Fab-scFv>scFv-scFv in HER2 3+ tumor cells.

[0563] The effect of anti-HER2 biparatopic antibody formats on survival of HER2+ cells is shown in FIG. **46**, where FIG. **46**A shows the result in the Trastuzumab sensitive SKOV3 HER2 2+/3+ cell line at 300 nM; FIG. **46**B shows the result in JIMT-1 HER2 2+(Trastuzumab resistant) cells at 300 nM, and FIG. **46**C shows the result in MCF7 HER2 1+ cell line at 300 nM. In the SKOV3 cell line, little difference was observed among the biparatopic formats in the extent of growth inhibition, and no growth inhibition was observed by any of the test antibodies in JIMT-1 and MCF7 cells.

[0564] The data in FIG. **44** and FIG. **45** show that anti-HER2 ECD2×ECD4 biparatopic antibodies with the Fab-scFv and Fab-Fab formats (v5019, v7091, v10000, v6903) are capable of growth inhibition HER2 3+ tumor cells in the absence, and presence of EGF or HRG. In the HER2 3+ cell lines BT-474 and SKBR3, growth inhibition relative to the mock control rank ordered as follows, where v506+ v4184>v6903>v7091>v10000>v5019>v506>v6717. The distance between antigen-binding domains (Fab-Fab>Fab-scFv>scFv-scFv) correlates with the rank order of growth inhibition in the HER2 3+ tumor cells. Based on the data in trastuzumab-sensitive tumor cells, BT-474, and SKBr3, it may be expected that the growth inhibition difference among formats is significant at the HER2 3+ level but less so at the HER2 2+ or HER2 1+ levels.

Example 43: Evaluation of HER2 Binding Affinity and Kinetic at Varying Antibody Capture Levels

[0565] The following experiment was conducted to compare HER2 binding kinetics (kd, off-rate) of exemplary anti-HER2 ECD2×ECD4 biparatopic antibodies when captured at varying surface densities by SPR. The correlation between a reduced (slower) off-rate with increasing antibody capture levels (surface density) is an indication of Trans binding (i.e. one antibody molecule binding to two HER2 molecules, described in Example 12). In this experiment the Fab-Fab format (v6903) was compared to the Fab-scFv format (v7091) to determine potential difference in Trans binding among the variants. Due to the larger spatial distance between antigen-binding domains, it is hypothesized that the Fab-Fab format may be capable of Cis binding (engaging ECD 2 and 4 on one HER2 molecule); whereas, the Fab-scFv would not capable of Cis binding due to the shorter distance between the it's antigen-binding domains. The anti-HER2 monospecific v506 was included as a control.

[0566] The experiment was conducted by SPR as described in Example 12. The data are shown in FIG. **47**. FIG. **47**A shows the plot and linear regression analysis for the kd (1/s) at different antibody capture levels with v6903 and v7091. Both v7091 and v6093 show a trend for decreasing off-rate with increasing surface capture levels; however, the correlation is significant with the Fab-scFv variant (v7091; P value=0.023) but not the Fab-Fab format (v6093; P value=0.053). The off-rate remained unchanged with varying antibody capture levels for the anti-HER2 monospecific control, v506.

[0567] FIG. **47**B shows the plot and linear regression analysis for the K_D (M) at different antibody capture levels with v6903 and v7091. Similar to the off-rate comparison, both v7091 and v6093 show a trend for increasing affinity (lower K_D value) with increasing surface capture levels. However, the correlation is significant with the Fab-scFv variant (v7091; P value=0.04) but not the Fab-Fab format (v6093; P value=0.51). The K_D remained unchanged with varying antibody capture levels for the anti-HER2 monospecific control, v506. The data in FIG. **47** shows that the Fab-Fab and Fab-scFv anti-HER2 biparatopic antibody formats show trends of decreasing off-rates with increasing antibody surface capture levels; these trends are unique compared to a monospecific anti-Her2 antibody.

Example 44: Affinity and Stability Engineering of the Pertuzumab Fab

[0568] As indicated in Table 1, one variant (v10000) contains mutations in the Pertuzumab Fab. This Fab was derived from affinity and stability engineering in silico efforts, which were measured experimentally as monovalent or One-Armed Antibodies (OAAs).

[0569] Variant 9996: a monovalent anti-HER2 antibody, where the HER2 binding domain is a Fab derived from pertuzumab on chain A, with Y96A in VL region and T30A/A49G/L69F in VH region (Kabat numbering) and the Fc region is a heterodimer having the mutations T350V_L351Y_F405A_Y407V (EU numbering) in Chain A, T350V_T366L_K392L_T394W (EU numbering) in Chain B, and the hinge region of Chain B having the mutation C226S; the antigen-binding domain binds to domain 4 of HER2.

[0570] Variant 10014: a monovalent anti-HER2 antibody, where the HER2 binding domain is a Fab derived from pertuzumab on chain A, with Y96A in VL region and T30A in VH region (Kabat numbering) and the Fc region is a heterodimer having the mutations T350V_L351Y_F405A_Y407V (EU numbering) in Chain A, T350V_T366L_K392L_T394W (EU numbering) in Chain B, and the hinge region of Chain B having the mutation C226S; the antigen-binding domain binds to domain 4 of HER2.

[0571] Variant 10013: a monovalent anti-HER2 antibody, where the HER2 binding domain is a Fab derived from wild type pertuzumab on chain A, and the Fc region is a heterodimer having the mutations T350V_L35 1Y_F405A_Y407V (EU numbering) in Chain A, T350V_T366L_K392L_T394W (EU numbering) in Chain B, and the hinge region of Chain B having the mutation C226S; the antigen-binding domain binds to domain 4 of HER2.

[0572] The following experiments were conducted to compare HER2 binding affinity and stability of the engineered Pertuzumab variants.

[0573] OAA variants were cloned and expressed as described in Example 1.

[0574] OAA were purified by protein A chromatography and Size Exclusion Chromatography, as described in Example 1.

[0575] Heterodimer purity (i.e. amount of OAA with a heterodimeric Fc) was assessed by non-reducing High Throughput Protein Express assay using Caliper LabChip GXII (Perkin Elmer #760499). Procedures were carried out according to HT Protein Express LabChip User Guide version2 LabChip GXII User Manual, with the following modifications. Heterodimer samples, at either 2 µl or 5 µl (concentration range 5-2000 ng/µ1), were added to separate wells in 96 well plates (BioRad # HSP9601) along with 7 µl of HT Protein Express Sample Buffer (Perkin Elmer #760328). The heterodimer samples were then denatured at 70° C. for 15 mins. The LabChip instrument is operated using the HT Protein Express Chip (Perkin Elmer #760499) and the Ab-200 assay setting. After use, the chip was cleaned with MilliQ water and stored at 4° C.

[0576] The stability of the samples was assessed by measuring melting temperature or Tm, as determined by DSC with the protocol shown in example 24. The DSC was measured before and after SEC purification.

[0577] The affinity towards HER2 ECD of the samples was measured by SPR following the protocol from example 12. The SPR was measured before and after SEC purification. As summarized in Table 47A and 47B, the mutations in the variable domain have increased the HER2 affinity of the Fab compared to wild type pertuzumab, while maintaining WT stability. ([1] Purity determined by Caliper LabChip; [2] KD(WT)/KD(mut)

TABLE 47A

				SPR pre-SEC				Het	SPR post-SEC			
OAA variant	Fab HC mutations	LC mut	Pr-A Yield (mg/L)	KD AVE (nM)	KD STDEV (nM)	n	Fold wrt WT[2]	purity post-SEC[1]	KD AVE (nM)	KD STDEV (nM)	n	Fold wrt WT
v9996	T30A/A49G/L69F	Y96A	22	1.7E−09	1.7E−10	5	9.6	93%	1.8E−09	1.6E−11	2	8.4
v10014	T30A	Y96A	20	2.0E−09	3.1E−10	4	8.1	81%	2.1E−09	5.2E−10	3	7.0
v10013	WT	WT	18	1.6E−08	5.1E−09	16	1.0	91%	1.5E−08	3.5E−09	4	1.0

TABLE 47B

	DSC pre-SEC		DSC post-SEC	
OAA variant	Tm (C.)	ΔTm wrt WT (C.)	Tm (C.)	ΔTm wrt WT (C.)
v9996	77.2	−0.2	77.2	−0.7
v10014	75.5	−1.9	75.5	−2.4
v10013	77.4	0.0	77.9	0.0

Example 45: Effect of v10000 on Survival and Tumor Growth in a Xenograft Model of HER2-Low, Non-Small Cell Lung Cancer (NSCLC)

[0578] This experiment was performed to assess efficacy of v10000 compared to control IgG (v6908) in an A549 xenograft model of lung cancer. A549 cells are derived from non-squamous non-small cell lung cancer that is HER2-low, non-HER2 gene amplified, HER3+, EGFR-low and moderately sensitive to Cisplatin at the MTD (maximum tolerated dose). The study was carried out as described below.

[0579] Tumor cell suspensions were implanted subcutaneously into athymic nude mice. When tumors reached 158 mm^3 the animals were randomly assigned to groups as shown in Table A1, and treatment began in a blinded and controlled study. Animals were treated according to Regimen 1 on Day 1, followed by treatment according to Regimen 2 on subsequent days as indicated in Table A1.

TABLE A1

Study Design								
	Regimen 1				Regimen 2			
Group (n)	Agent	Dosage (mg/kg)	Route	Schedule	Agent	Dosage (mg/kg)	Route	Schedule
1 (20)	v6908	15	iv	Day 1	v6908	10	iv	Days 4, 8, 11, 15, 18, 22 and 25
2 (20)	v10000	15	iv	Day 1	v10000	10	iv	Days 4, 8, 11, 15, 18, 22 and 25

[0580] Tumor volume was measured by calipers twice weekly. The study duration was 66 days with survival as the primary endpoint. Additional tumor response criteria were measured and are shown in Table A2. Mice were euthanized when tumor volume exceeded 800 mm^3, the surviving percentage versus study day was plotted on a Kaplan-Meier and was statistically assessed using a log-rank test. Serum concentration of v10000 was determined by HER2 ELISA on study day 7.

[0581] The results are shown in FIG. **48**A (tumor volume) and FIG. **48**B (Kaplan-Meier survival). Variant 10000 reduced tumor growth compared to v6908 treated controls and significantly prolonged survival by log-rank test (FIG. **48**B and Table A3). Animals treated with v10000 had a median survival of greater than 66 days while those treated with v6908 had a median survival of 25.78 days (FIG. **48**B and Table A2). Tumor volume on study day 30 was 461 mm3 and 810 mm3 for v10000 and v6908 treated groups respectively (FIG. **48**A and Table A2). Serum exposure was 140.9 microg/mL on study day 7, indicating that the anticipated serum concentration was achieved.

[0582] These results show that treatment with v10000 was able to reduce tumor growth and prolong survival compared to treatment with a control hIgG in this HER2-low non-gene amplified NSCLC model.

TABLE A2

A549 Tumor Response Profile		
	6908	10000
Tumor Response on Day 30		
Mean TV (mm^3) (% Δ from base line)	810 (413%)	461 (191%)
Treatment/Control Ratio	1.00	0.57
RECIST Scores		
CR (TV <20 mm^3)	0/20	0/20
PR (>30% baseline regression)	0/20	1/20
PD (>20% baseline growth)	20/20	19/20
SD (neither PD or PR)	0/20	0/20
Median Time to Progression (days)	3.30	2.31

TABLE A2-continued

A549 Tumor Response Profile		
	6908	10000
Survival Response		
Median Survival (days)	25.78	>66

CR—Complete Response
PR—Partial Response
PD—Progressive Disease
SD—Stable Disease

TABLE A3

Log Rank Summary	
Group	6908
6908	—
10000	★★★

Legend:
ns = not significant,
★ = P < 0.05.
★★ = P < 0.01,
★★★ = P < 0.001

Example 46: Effect of v10000 on Survival and Tumor Growth in a Xenograft Model of HER2-Low, Head and Neck Squamous Cell Carcinoma

[0583] This experiment was performed to assess efficacy of v10000 compared to Herceptin™ (v6336) and control human IgG (v6908) in the FaDu xenograft model of head and neck cancer. FaDu cells are derived from squamous cell cancer of the head and neck that is HER2 low, non-HER2 gene amplified, HER3+, EGFR+ and highly sensitive to Cisplatin at the MTD. The study was carried out as described below.

[0584] Tumor cell suspensions were implanted subcutaneously into athymic nude mice. When tumors reached 121 mm^3 the animals were randomly assigned to groups as shown in Table A4, and treatment began in a blinded and controlled study. Cisplatin was purchased and provided for the study by Charles River Laboratories (Morrisville, N.C.). Animals were treated according to Regimen 1 at Day 1, followed by Regimen 2 on subsequent days as noted in Table A4.

TABLE A4

Study Design								
	Regimen 1				Regimen 2			
Group (n)	Agent	Dosage (mg/kg)	Route	Schedule	Agent	Dosage (mg/kg)	Route	Schedule
1 (15)	v6908	15	iv	Day 1	v6908	10	iv	Days 4, 8, 11, 15, 18, 22 and 25
2 (15)	v6336	15	iv	Day 1	v6336	10	iv	Days 4, 8, 11, 15, 18, 22 and 25
3 (15)	v10000	15	iv	Day 1	v10000	10	iv	Days 4, 8, 11, 15, 18, 22 and 25
4 (15)	Cisplatin	2	ip	Day 1, 3, 5, 7, 9, 11				

TABLE A4-continued

Study Design								
	Regimen 1				Regimen 2			
Group (n)	Agent	Dosage (mg/kg)	Route	Schedule	Agent	Dosage (mg/kg)	Route	Schedule
5 (15)	v10000	15	iv	Day 1	v10000	10	iv	Days 4, 8, 11, 15, 18, 22 and 25
	Cisplatin	2	ip	Day 1, 3, 5, 7, 9, 11				

[0585] Tumor volume was measured by calipers twice weekly. The study duration was 59 days with survival as the primary endpoint. Additional tumor response criteria were measured and are shown in Table A5. Mice were euthanized when tumor volume exceeded 2000 mm^3, the surviving percentage versus study day was plotted on a Kaplan-Meier and was statistically assessed using a log-rank test. Serum concentration of v10000 and v6336 was determined by HER2 ELISA on study day 7.

[0586] The results are shown in FIG. **49**A (tumor volume) and FIG. **49**B (Kaplan-Meier survival). Variant 10000 reduced tumor growth compared to v6908 treated controls and v6336, as well as significantly prolonged survival by log-rank test compared to v6908 (FIG. **48**B and Table A3). Animals treated with v10000 had a median survival of greater than 46 days while those treated with v6908 and v6336 had median survivals of 25 and 40 days, respectively (FIG. **49**B and Table A5). Tumor volume on study day 25 was 1025, 1979, 1257 mm^3 for v10000, v6908 and v6336 treated groups respectively (FIG. **49**A and Table A5). Serum exposure was 116.6 microg/mL for v10000, 119.9 microg/mL for v6336, and 107.2 microg/mL for v10000+Cisplatin on study day 7, indicating that the anticipated serum concentration was achieved for each test article.

[0587] These results show that treatment with v10000 as a monotherapy was able to decrease tumor volume and prolong survival, compared to treatment with control IgG in this model of HER2-low non-gene amplified head and neck cancer. Overall, v10000 showed a trend towards decreasing tumor volume compared to v6336 (Herceptin™).

[0588] Variant 10000 was also tested in combination with cisplatin. The combination of v10000 and cisplatin significantly prolonged survival compared to v6908, v6336, and single agent cisplatin (Table A5). The median survival of the v10000 and cisplatin combination was 53 days while the median survival of v6908, v6336, and single agent cisplatin was 25, 40, and 40 days, respectively.

[0589] These results demonstrate that treatment with v10000 in combination with cisplatin was able to decrease tumor growth and prolong survival compared to v6908 and v6336, in this model of head and neck cancer.

TABLE A5

FaDu Tumor Response Profile					
	6908	6336	10000	cisplatin	10000 + cisplatin
Tumor Response on Day 25					
Mean TV (mm^3) (% Δ from base line)	1979 (1532%)	1257 (929%)	1025 (782%)	1070 (782%)	816 (573%)
Treatment/Control Ratio	1.00	0.63	0.52	0.54	0.41
RECIST Scores					
CR (TV <20 mm^3)	0/15	0/14	0/15	0/15	0/15
PR (>30% baseline regression)	0/15	0/14	0/15	0/15	0/15
PD (>20% baseline growth)	15/15	14/14	15/15	15/15	15/15
SD (neither PD or PR)	0/15	0/15	0/15	0/15	0/15
Median Time to Progression (days)	5.9	7.6	7.8	8.4	10.8
Survival Response					
Median Survival (days)	25	40	46	40	53

CR—Complete Response

PR—Partial Response

PD—Progressive Disease

SD—Stable Disease

TABLE A6

Log Rank Summary

Group	6908	6336	10000	Cisplatin
6908	—	—	—	—
6336	★★	—	—	—
10000	★★★	n/s	—	—
Cisplatin	★★★	n/s	★	—
10000 + Cisplatin	★★★	★	n/s	★★★

Legend:
ns = not significant,
★ = P < 0.05.
★★ = P < 0.01,
★★★ = P < 0.001

Example 47: Effect of v10000 on Survival and Tumor Growth Inhibition in a Xenograft Model of HER2 1+, ER+ Breast Cancer

[0590] This experiment was performed to assess efficacy of v10000 compared to a control IgG (v6908) or Herceptin™ (v6336) in the ST1337B xenograft model of breast cancer. ST1337B is a patient derived xenograft (PDX) established in nude mice from an ER+/PR− breast cancer with a luminal B molecular classification. ST1337 is HER2 1+ as measured by IHC. The study was carried out as described below.

[0591] Tumor fragments were implanted subcutaneously into athymic nude mice. When tumors reached 180 mm^3 the animals were randomly assigned to groups as shown in Table A7 and treatment began in a blinded and controlled study. Animals were treated according to Regimen 1 as shown in Table A7

TABLE A7

Study Design

		Regimen 1		
Group (n)	Agent	Dosage (mg/kg)	Route	Schedule
1 (15)	v6908	30	iv	Days 1,4, 8, 11, 15, 18, 22, 25, 28, and 32
2 (15)	V6336	10	iv	Days 1, 4, 8, 11, 15, 18, 22, 25, 28, and 32

TABLE A7-continued

Study Design

		Regimen 1		
Group (n)	Agent	Dosage (mg/kg)	Route	Schedule
3 (15)	v10000	3	iv	Days 1, 4, 8, 11, 15, 18, 22, 25, 28, and 32
4 (15)	v10000	10	iv	Days 1, 4, 8, 11, 15, 18, 22, 25, 28, and 32
5 (15)	v10000	30	iv	Days 1, 4, 8, 11, 15, 18, 22, 25, 28, and 32

[0592] Tumor volume was measured by calipers twice weekly. The study duration was 63 days with survival as the primary endpoint. Additional tumor response criteria were measured and are shown in Table A8. Mice were euthanized when tumor volume exceeded 2000 mm^3, the surviving percentage versus study day was plotted on a Kaplan-Meier and was statistically assessed using a log-rank test. Serum concentration of v10000 and v6336 was determined by HER2 ELISA on study day 7 and on day 36, 4 days following the last dose on day 32.

[0593] The results are shown in FIG. **50**A (tumor volume) and FIG. **50**B (Kaplan-Meier survival). Treatment with variant 10000 at all doses tested reduced tumor growth compared to treatment with v6908 and significantly prolonged survival by log-rank test compared to v6908 (FIG. **50**B and Table A9). In addition, treatment with v10000 at 30 mg/kg significantly prolonged survival compared to treatment with v6336 at 10 mg/kg (FIG. **50**B and Table A8). Animals treated with v10000 had median survivals of 49, 59, and 59 days for the 3, 10 and 30 mg/kg doses respectively (FIG. **50**B and Table A8). Tumor volume on study day 29 for treatment with v10000 at 3, 10 and 30 mg/kg was 1010, 1016, and 931 mm3, respectively. Tumor volumes for v6908 and v6336 on study day 29 was 1898 and 1264 mm3 respectively (FIG. **50**A and Table A8). The serum exposure of v6336 and v10000 is shown in Table A10. These results confirm that increasing the dosage of v10000 results in an increase in serum concentration of v10000, and that similar doses of v10000 and v6336 result in similar serum concentrations of antibody.

[0594] These results indicate that treatment with v10000 is able to decrease tumor volume and prolong survival in this model of HER2-low ER+ breast cancer, when compared to the IgG control and to Herceptin™.

TABLE A8

ST1337b Tumor Response Profile

	6908, 30 mg/kg	6336, 10 mg/kg	10000, 3 mg/kg	10000, 10 mg/kg	10000, 30 mg/kg
Tumor Response on Day 29					
Mean TV (mm^3) (% Δ from base line)	1898 (953%)	1264 (601%)	1010 (460%)	1016 (457%)	931 (411%)
Treatment/Control Ratio	1.00	0.66	0.53	0.53	0.49
RECIST Scores					
CR (TV <20 mm^3)	0/15	0/15	0/15	0/15	0/15
PR (>30% baseline regression)	0/15	0/15	0/15	0/15	0/15
PD (>20% baseline growth)	15/15	15/15	15/15	15/15	15/15
SD (neither PD or PR)	0/15	0/15	0/15	0/15	0/15
Median Time to Progression (days)	11	10	14	26	13

TABLE A8-continued

ST1337b Tumor Response Profile					
	6908, 30 mg/kg	6336, 10 mg/kg	10000, 3 mg/kg	10000, 10 mg/kg	10000, 30 mg/kg
Survival Response					
Median Survival (days)	29	43	49	59	59

CR—Complete Response
PR—Partial Response
PD—Progressive Disease
SD—Stable Disease

TABLE A9

Log Rank Summary					
Group	6908, 30 mg/kg	6336, 10 mg/kg	10000, 3 mg/kg	10000, 10 mg/kg	10000, 30 mg/kg
6908, 30 mg/kg	—	—	—	—	
6336, 10 mg/kg	★★	—	—	—	—
10000, 3 mg/kg	★★	n/s	—	—	—
10000, 10 mg/kg	★★★	n/s	n/s	—	—
10000, 30 mg/kg	★★★	★	n/s	n/s	—

Legend:
ns = not significant,
★ = P < 0.05.
★★ = P < 0.01,
★★★ = P < 0.001

TABLE A10

Serum Exposure Summary				
Sample Day	6336, 10 mg/kg	10000, 3 mg/kg	10000, 10 mg/kg	10000, 30 mg/kg
7	133.0	30.7	101.7	286.6
36	135.2	46.0	186.3	279.7

Example 48: Effect of v10000 on Survival and Tumor Growth Inhibition in a Xenograft Model of HER2 Negative Pancreatic Cancer

[0595] This experiment was performed to assess efficacy of v10000 compared to a control IgG (v12470), Herceptin™ (v6336), and nab-paclitaxel as single agents and v10000 in combination with nab-paclitaxel (Abraxane™ Celgene) in the ST803 xenograft model of pancreatic cancer. ST803 is a patient-derived xenograft (PDX) of pancreatic cancer (South Texas Accelerated Research Therapeutics, San Antonio, Tex. 78229) that is HER2 negative as measured by IHC. The study was carried out as described below.

[0596] Tumor fragments were implanted subcutaneously into athymic nude mice. When tumors reached 170 mm^3 the animals were randomly assigned to groups as shown in Table All and treatment began in a blinded and controlled study. Animals were treated according to Regimen 1 and 2 as shown in Table A11. All treatments were administered intravenously.

TABLE A11

Study Design						
	Regimen 1			Regimen 2		
Group (n)	Agent	Dosage (mg/kg)	Schedule	Agent	Dosage (mg/kg)	Schedule
1 (20)	v12470	30	Twice weekly for four weeks			
2 (20)	V6336	30	Twice weekly for four weeks			
3 (20)	v10000	30	Twice weekly for four weeks			
4 (20)	v12470	30	Twice weekly for four weeks	nab-paclitaxel	30	Days 2, 9, 16
5 (20)	v10000	30	Twice weekly for four weeks	nab-paclitaxel	30	Days 2, 9, 16

[0597] Tumor volume was measured by calipers twice weekly. The study duration was 71 days with survival as the primary endpoint. Additional tumor response criteria were measured and are shown in Table A12. Mice were euthanized when tumor volume exceeded 2000 mm^3; the surviving percentage versus study day was plotted on a Kaplan-Meier and was statistically assessed using a log-rank test. Serum concentration in groups dosed with v10000 and v6336 was determined by HER2 ELISA on study day 7.

[0598] The results are shown in FIG. **51**A (tumor volume) and FIG. **51**B (Kaplan-Meier survival). Only treatment with variant 10000 in combination with nab-paclitaxel reduced tumor growth and significantly prolonged survival by log-rank test compared to treatment with control IgG (v12470) (FIG. **51**B and Table A13). In addition, treatment with v10000 in combination with nab-paclitaxel significantly prolonged survival compared to treatment with nab-paclitaxel plus control IgG (FIG. **51**B and Table A13). The median survival of v10000 in combination with nab-paclitaxel was greater than 71 days while the median survival of v12470, v6336, v10000, and nab-paclitaxel as single agents was 58.8, 65.9, 69.3, and 60.6 days respectively. Mean tumor volume on study day 54 for treatment with v10000 in combination with nab-paclitaxel was 1073 mm3. Tumor volumes for v12470, v6336, v10000, and nab-paclitaxel as single agents on study day 54 was 1663, 1494, 1305, and 1365 mm3 respectively (FIG. **51**A and Table A12). The serum exposure of v6336 and v10000 from day 14 serum samples is shown in Table A14.

[0599] These results indicate that treatment with v10000 in combination with nab-paclitaxel is able to decrease tumor volume and prolong survival in this model of HER2 negative pancreatic cancer, when compared to the IgG control, Herceptin™, and single agent v10000.

TABLE A12

ST803 Tumor Response Profile

	12470	6336	10000	12470 + nab-pac*	12470 + nab-pac*
Tumor Response on Day 54					
Mean TV (mm^3) (% Δ from base line)	1663 (+888%)	1494 (+806%)	1305 (+659%)	1365 (+693%)	1073 (+522%)
Treatment/Control Ratio	1.00	0.90	0.78	0.82	0.64
RECIST Scores					
CR (TV <20 mm^3)	0/18	0/17	0/20	0/16	0/19
PR (>30% baseline regression)	0/18	0/17	0/20	0/16	0/19
PD (>20% baseline growth)	18/18	17/17	20/20	16/16	19/19
SD (neither PD or PR)	0/18	0/17	0/20	0/16	0/19
Median Time to Progression (days)	4.4	3.6	3.6	4.4	5.6
Survival Response					
Median Survival (days)	58.8	65.9	69.3	60.6	>71

CR—Complete Response
PR—Partial Response
PD—Progressive Disease
SD—Stable Disease
*nab-paclitaxel

TABLE A13

Log Rank Summary

Group	12470	6336	10000	12470 + nab-pac*	10000 + nab-pac*
12470	—	—	—	—	
6336	ns	—	—	—	—
10000	ns	ns	—	—	—
12470 + nab-pac	ns	—	Ns	—	—
10000, + nab-pac	★★	—	Ns	★★	—

Legend:
ns = not significant,
★ = P < 0.05.
★★ = P < 0.01,
★★★ = P < 0.001
*nab-paclitaxel

TABLE A14

Serum Exposure Summary

Sample Day	6336 (microg/mL)	10000 (microg/mL)	10000 (microg/mL) + nab-paclitaxel
14	426.7	279	391

Example 49: Effect of v10000 on Tumor Growth Inhibition in a Xenograft Model of HER2 3+ Gastric Cancer

[0600] This experiment was performed to assess efficacy of v10000 compared to a control IgG (v12470) and Herceptin™ (v6336) as single agents in the GXA3054 xenograft model of gastric cancer. GXA3054 is a patient derived xenograft (PDX) of gastric cancer that is HER2 3+ (Oncotest GmbH, Am Flughafen 12-14, 79108 Freiburg, Germany). The study was carried out as described below.

[0601] Tumor fragments were implanted subcutaneously into athymic nude mice. When tumors reached 144 mm^3 the animals were randomly assigned to groups as shown in Table A15 and treatment began in a blinded and controlled study. Animals were treated according to Regimen 1 as shown in Table A15.

TABLE A15

Study Design

Regimen 1

Group (n)	Agent	Dosage (mg/kg)	Route	Schedule
1 (10)	v12470	30	IV	Twice weekly for five weeks
2 (10)	V6336	30	IV	Twice weekly for five weeks
3 (10)	v10000	30	IV	Twice weekly for five weeks

[0602] Tumor volume was measured by calipers twice weekly. The study duration was 59 days with tumor growth inhibition as the primary endpoint. Additional tumor response criteria were measured and are shown in Table A16. Mice were euthanized when tumor volume exceeded 2000 mm^3.

[0603] The results are shown in FIG. **52** (tumor volume). Treatment with variant 10000 and v6336 reduced tumor growth compared to treatment with control IgG (v12470) (FIG. **52** and Table A16). In addition, treatment with v10000 reduced tumor growth compared to treatment with v6336 (FIG. **52** and Table A16). Mean tumor volume on study day 35 for treatment with control IgG, v10000 and v6336 was 1340, 236, and 7.8 mm3, respectively. Tumor growth inhibition on day 35 for v10000 and v6336 was 111 and 92%, respectively (Table A16). On day 35 tumors treated with v10000 showed greater responses (7/10 complete and 3/10 partial responses) compared to tumors treated with v6336 (0/10 complete and 1/10 partial response) (Table A16). At the completion of the study, on day 59, 9/10 tumors treated with v10000 had complete responses with no evidence of recurrent tumor, while for v6336 treated tumors only 1/10 tumors had a complete response.

[0604] These results indicate that treatment with v10000 can regress tumors in this model of HER2 3+ gastric cancer. The tumor growth inhibition of v10000 was superior to IgG control and Herceptin™.

TABLE A16

GXA3054 Tumor Response Profile

	12470	6336	10000
Tumor Response on Day 35 Tumor Growth Inhibition (%) RECIST Scores	Na	92	111
CR (≤−95%)	0/10	0/10	7/10
PR (>−95% and <−66%)	0/10	1/10	3/10
SD (≥−66% and ≤+73%)	0/10	5/10	0/10
PD (>+73%)	10/10	4/10	0/10

CR—Complete Response
PR—Partial Response
PD—Progressive Disease
SD—Stable Disease

[0605] The reagents employed in the examples are generally commercially available or can be prepared using commercially available instrumentation, methods, or reagents known in the art. The foregoing examples illustrate various aspects described herein and practice of the methods described herein. The examples are not intended to provide an exhaustive description of the many different embodiments of the invention. Thus, although the forgoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, those of ordinary skill in the art will realize readily that many changes and modifications can be made thereto without departing from the spirit or scope of the appended claims.

[0606] All publications, patents and patent applications mentioned in this specification are herein incorporated by reference into the specification to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated herein by reference.

SEQUENCE TABLE

Variant	Ht clone name	H2 clone name	L1 clone name	L2 clone name
792	1011	1015	-2	-2
5019	3057	720	1811	NA
5020	719	3041	NA	1811
7091	3057	5244	1811	NA
10000	6586	5244	3382	NA
6903	5065	3468	5037	3904
6902	5065	3468	5034	3904
6717	3317	720	NA	NA
1040	4560	4553	NA	4561
630	719	716	NA	NA
4182	4560	3057	NA	1811
506	642	642	-2	-2
4184	3057	3041	1811	1811
9996	4372	6586	NA	3382

SEQ ID NO.	Clone	Desc.	Sequence (amino acid or
1	642	Full	EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTISADT SKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKS CDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL SLSPGK
2	642	Full	GAGGTGCAGCTGGTGGAAAGCGGAGGAGGACTGGTGCAGCCAGGAGGATCTCTGCGACTGAGTTGCGCCGCTTC AGGATTCAACATCAAGGACACCTACATTCACTGGGTGCGACAGGCTCCAGGAAAAGGACTGGAGTGGGTGGCTC GAATCTATCCCACTAATGGATACACCCGGTATGCCGACTCCGTGAAGGGGAGGTTTACTATTAGCGCCGATACA TCCAAAAACACTGCTTACCTGCAGATGAACAGCCTGCGAGCCGAAGATACCGCTGTGTACTATTGCAGTCGATG GGGAGGAGACGGATTCTACGCTATGGATTATTGGGGACAGGGGACCCTGGTGACAGTGAGCTCCGCCTCTACCA AGGGCCCCAGTGTGTTTCCCCTGGCTCCTTCTAGTAAATCCACCTCTGGAGGGACAGCCGCTCTGGGATGTCTG

SEQUENCE TABLE-continued

			GTGAAGGACTATTTCCCCGAGCCTGTGACCGTGAGTTGGAACTCAGGCGCCCTGACAAGCGGAGTGCACACTTT TCCTGCTGTGCTGCAGTCAAGCGGGCTGTACTCCCTGTCCTCTGTGGTGACAGTGCCAAGTTCAAGCCTGGGCA CACAGACTTATATCTGCAACGTGAATCATAAGCCCTCAAATACAAAAGTGGACAAGAAAGTGGAGCCCAAGAGC TGTGATAAGACCCACACCTGCCCTCCCTGTCCAGCTCCAGAACTGCTGGGAGGACCTAGCGTGTTCCTGTTTCC CCCTAAGCCAAAAGACACTCTGATGATTTCCAGGACTCCCGAGGTGACCTGCGTGGTGGTGGACGTGTCTCACG AGGACCCCGAAGTGAAGTTCAACTGGTACGTGGATGGCGTGGAAGTGCATAATGCTAAGACAAAACCAAGAGAG GAACAGTACAACTCCACTTATCGCGTCGTGAGCGTGCTGACCGTGCTGCACCAGGACTGGCTGAACGGGAAGGA GTATAAGTGCAAAGTCAGTAATAAGGCCCTGCCTGCTCCAATCGAAAAAACCATCTCTAAGGCCAAAGGCCAGC CAAGGGAGCCCCAGGTGTACACACTGCCACCCAGCAGAGACGAACTGACCAAGAACCAGGTGTCCCTGACATGT CTGGTGAAAGGCTTCTATCCTAGTGATATTGCTGTGGAGTGGGAATCAAATGGACAGCCAGAGAACAATTACAA GACCACACCTCCAGTGCTGGACAGCGATGGCAGCTTCTTCCTGTATTCCAAGCTGACAGTGGATAAATCTCGAT GGCAGCAGGGGAACGTGTTTAGTTGTTCAGTGATGCATGAAGCCCTGCACAATCATTACACTCAGAAGAGCCTG TCCCTGTCTCCCGGCAAA
3	642	VH	EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTISADT SKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSS
4	642	VH	GAGGTGCAGCTGGTGGAAAGCGGAGGAGGACTGGTGCAGCCAGGAGGATCTCTGCGACTGAGTTGCGCCGCTTC AGGATTCAACATCAAGGACACCTACATTCACTGGGTGCGACAGGCTCCAGGAAAAGGACTGGAGTGGGTGGCTC GAATCTATCCCACTAATGGATACACCCGGTATGCCGACTCCGTGAAGGGGAGGTTTACTATTAGCGCCGATACA TCCAAAAACACTGCTTACCTGCAGATGAACAGCCTGCGAGCCGAAGATACCGCTGTGTACTATTGCAGTCGATG GGGAGGAGACGGATTCTACGCTATGGATTATTGGGGACAGGGGACCCTGGTGACAGTGAGCTCC
5	642	H1	GFNIKDTY
6	642	H1	GGATTCAACATCAAGGACACCTAC
7	642	H3	SRWGGDGFYAMDY
8	642	H3	AGTCGATGGGGAGGAGACGGATTCTACGCTATGGATTAT
9	642	H2	IYPTNGYT
10	642	H2	ATCTATCCCACTAATGGATACACC
11	642	CH1	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHKPSNTKVDKKV
12	642	CH1	GCCTCTACCAAGGGCCCCAGTGTGTTTCCCCTGGCTCCTTCTAGTAAATCCACCTCTGGAGGGACAGCCGCTCT GGGATGTCTGGTGAAGGACTATTTCCCCGAGCCTGTGACCGTGAGTTGGAACTCAGGCGCCCTGACAAGCGGAG TGCACACTTTTCCTGCTGTGCTGCAGTCAAGCGGGCTGTACTCCCTGTCCTCTGTGGTGACAGTGCCAAGTTCA AGCCTGGGCACACAGACTTATATCTGCAACGTGAATCATAAGCCCTCAAATACAAAAGTGGACAAGAAAGTG
13	642	CH2	APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK
14	642	CH2	GCTCCAGAACTGCTGGGAGGACCTAGCGTGTTCCTGTTTCCCCCTAAGCCAAAAGACACTCTGATGATTTCCAG GACTCCCGAGGTGACCTGCGTGGTGGTGGACGTGTCTCACGAGGACCCCGAAGTGAAGTTCAACTGGTACGTGG ATGGCGTGGAAGTGCATAATGCTAAGACAAAACCAAGAGAGGAACAGTACAACTCCACTTATCGCGTCGTGAGC GTGCTGACCGTGCTGCACCAGGACTGGCTGAACGGGAAGGAGTATAAGTGCAAAGTCAGTAATAAGGCCCTGCC TGCTCCAATCGAAAAAACCATCTCTAAGGCCAAA
15	642	CH3	GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
16	642	CH3	GGCCAGCCAAGGGAGCCCCAGGTGTACACACTGCCACCCAGCAGAGACGAACTGACCAAGAACCAGGTGTCCCT GACATGTCTGGTGAAAGGCTTCTATCCTAGTGATATTGCTGTGGAGTGGGAATCAAATGGACAGCCAGAGAACA ATTACAAGACCACACCTCCAGTGCTGGACAGCGATGGCAGCTTCTTCCTGTATTCCAAGCTGACAGTGGATAAA TCTCGATGGCAGCAGGGGAACGTGTTTAGTTGTTCAGTGATGCATGAAGCCCTGCACAATCATTACACTCAGAA GAGCCTGTCCCTGTCTCCCGGC
17	3468	Full	EVQLVESGGGLVQPGGSLRLSCAASGFTFTDYTMDWVRQAPGKGLEWVADVNPNSGCSIYNQRFKGRFTLSVDR SKNTLYLQMNSLRAEDTAVYYCARNLGPSFYFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KGYFPEPVTVSWNSGALTSGVHTFPAVLKSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYVLPPSRDELTKNQVSLLCL VKGFYPSDIAVEWESNGQPENNYLTWPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
18	3468	Full	GAAGTGCAGCTGGTCGAATCTGGAGGAGGACTGGTGCAGCCAGGAGGGTCCCTGCGCCTGTCTTGCGCCGCTAG TGGCTTCACTTTTACCGACTACACCATGGATTGGGTGCGACAGGCACCTGGAAAGGGCCTGGAGTGGGTCGCCG ATGTGAACCCAAATAGCGGAGGCTCCATCTACAACCAGCGGTTCAAGGGCCGGTTCACCCTGTCAGTGGACCGG AGCAAAAACACCCTGTATCTGCAGATGAATAGCCTGCGAGCCGAAGATACTGCTGTGTACTATTGCGCCCGGAA TCTGGGGCCCTCCTTCTACTTTGACTATTGGGGGCAGGGAACTCTGGTCACCGTGAGCTCCGCCTCCACCAAGG GACCTTCTGTGTTCCCACTGGCTCCCTCTAGTAAATCCACATCTGGGGGAACTGCAGCCCTGGGCTGTCTGGTG AAGGGCTACTTCCCAGAGCCCGTCACAGTGTCTTGGAACAGTGGCGCTCTGACTTCTGGGGTCCACACCTTTCC TGCAGTGCTGAAGTCAAGCGGGCTGTACAGCCTGTCCTCTGTGGTCACCGTGCCAAGTTCAAGCCTGGGAACAC

SEQUENCE TABLE-continued

			AGACTTATATCTGCAACGTGAATCACAAGCCATCCAATACAAAAGTCGACAAGAAAGTGGAACCCAAGTCTTGT GATAAAACCCATACATGCCCCCCTTGTCCTGCACCAGAGCTGCTGGGAGGACCAAGCGTGTTCCTGTTTCCACC CAAGCCTAAAGATACACTGATGATTAGTAGGACCCCAGAAGTCACATGCGTGGTCGTGGACGTGAGCCACGAGG ACCCCGAAGTCAAGTTTAACTGGTACGTGGACGGCGTCGAGGTGCATAATGCCAAGACTAAACCCAGGGAGGAA CAGTACAACAGTACCTATCGCGTCGTGTCAGTCCTGACAGTGCTGCATCAGGATTGGCTGAACGGGAAAGAGTA TAAGTGCAAAGTGAGCAATAAGGCTCTGCCCGCACCTATCGAGAAAACAATTTCCAAGGCAAAAGGACAGCCTA GAGAACCACAGGTGTACGTGCTGCCTCCATCAAGGGATGAGCTGACAAAGAACCAGGTCAGCCTGCTGTGTCTG GTGAAAGGATTCTATCCCTCTGACATTGCTGTGGAGTGGGAAAGTAATGGCCAGCCTGAGAACAATTACCTGAC CTGGCCCCCTGTGCTGGACTCAGATGGCAGCTTCTTTCTGTATAGCAAGCTGACCGTCGACAAATCCCGGTGGC AGCAGGGGAATGTGTTTAGTTGTTCAGTCATGCACGAGGCACTGCACAACCATTACACCCAGAAGTCACTGTCA CTGTCACCAGGG
19	3468	VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFTDYTMDWVRQAPGKGLEWVADVNPNSGCSIYNQRFKGRFTLSVDR SKNTLYLQMNSLRAEDTAVYYCARNLGPSFYFDYWGQGTLVTVSS
20	3468	VH	GAAGTGCAGCTGGTCGAATCTGGAGGAGGACTGGTGCAGCCAGGAGGGTCCCTGCGCCTGTCTTGCGCCGCTAG TGGCTTCACTTTTACCGACTACACCATGGATTGGGTGCGACAGGCACCTGGAAAGGGCCTGGAGTGGGTCGCCG ATGTGAACCCAAATAGCGGAGGCTCCATCTACAACCAGCGGTTCAAGGGCCGGTTCACCCTGTCAGTGGACCGG AGCAAAAACACCCTGTATCTGCAGATGAATAGCCTGCGAGCCGAAGATACTGCTGTGTACTATTGCGCCCGGAA TCTGGGGCCCTCCTTCTACTTTGACTATTGGGGGCAGGGAACTCTGGTCACCGTGAGCTCC
21	3468	H1	GFTFTDYT
22	3468	H1	GGCTTCACTTTTACCGACTACACC
23	3468	H3	ARNLGPSFYFDY
24	3468	H3	GCCCGGAATCTGGGGCCCTCCTTCTACTTTGACTAT
25	3468	H2	VNPNSGGS
26	3468	H2	GTGAACCCAAATAGCGGAGGCTCC
27	3468	CH1	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKGYFPEPVTVSWNSGALTSGVHTFPAVLKSSGLYSLSSVVTVPSS SLGTQTYICNVNHKPSNTKVDKKV
28	3468	CH1	GCCTCCACCAAGGGACCTTCTGTGTTCCCACTGGCTCCCTCTAGTAAATCCACATCTGGGGGAACTGCAGCCCT GGGCTGTCTGGTGAAGGGCTACTTCCCAGAGCCCGTCACAGTGTCTTGGAACAGTGGCGCTCTGACTTCTGGGG TCCACACCTTTCCTGCAGTGCTGAAGTCAAGCGGGCTGTACAGCCTGTCCTCTGTGGTCACCGTGCCAAGTTCA AGCCTGGGAACACAGACTTATATCTGCAACGTGAATCACAAGCCATCCAATACAAAAGTCGACAAGAAAGTG
29	3468	CH2	APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK
30	3468	CH2	GCACCAGAGCTGCTGGGAGGACCAAGCGTGTTCCTGTTTCCACCCAAGCCTAAAGATACACTGATGATTAGTAG GACCCCAGAAGTCACATGCGTGGTCGTGGACGTGAGCCACGAGGACCCCGAAGTCAAGTTTAACTGGTACGTGG ACGGCGTCGAGGTGCATAATGCCAAGACTAAACCCAGGGAGGAACAGTACAACAGTACCTATCGCGTCGTGTCA GTCCTGACAGTGCTGCATCAGGATTGGCTGAACGGGAAAGAGTATAAGTGCAAAGTGAGCAATAAGGCTCTGCC CGCACCTATCGAGAAAACAATTTCCAAGGCAAAA
31	3468	CH3	GQPREPQVYVLPPSRDELTKNQVSLLCLVKGFYPSDIAVEWESNGQPENNYLTWPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
32	3468	CH3	GGACAGCCTAGAGAACCACAGGTGTACGTGCTGCCTCCATCAAGGGATGAGCTGACAAAGAACCAGGTCAGCCT GCTGTGTCTGGTGAAAGGATTCTATCCCTCTGACATTGCTGTGGAGTGGGAAAGTAATGGCCAGCCTGAGAACA ATTACCTGACCTGGCCCCCTGTGCTGGACTCAGATGGCAGCTTCTTTCTGTATAGCAAGCTGACCGTCGACAAA TCCCGGTGGCAGCAGGGGAATGTGTTTAGTTGTTCAGTCATGCACGAGGCACTGCACAACCATTACACCCAGAA GTCACTGTCACTGTCACCAGGG
33	1811	Full	DIQMTQSPSSLSASVGDRVTITCKASQDVSIGVAWYQQKPGKAPKLLIYSASYRYTGVPSRFSGSGSGTDFTLT ISSLQPEDFATYYCQQYYIYPYTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQW KVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
34	1811	Full	GATATTCAGATGACCCAGTCCCCAAGCTCCCTGAGTGCCTCAGTGGGCGACCGAGTCACCATCACATGCAAGGC TTCCCAGGATGTGTCTATTGGAGTCGCATGGTACCAGCAGAAGCCAGGCAAAGCACCCAAGCTGCTGATCTATA GCGCCTCCTACCGGTATACCGGCGTGCCCTCTAGATTCTCTGGCAGTGGGTCAGGAACAGACTTTACTCTGACC ATCTCTAGTCTGCAGCCTGAGGATTTCGCTACCTACTATTGCCAGCAGTACTATATCTACCCATATACCTTTGG CCAGGGGACAAAAGTGGAGATCAAGAGGACTGTGGCCGCTCCCTCCGTCTTCATTTTTCCCCCTTCTGACGAAC AGCTGAAAAGTGGCACAGCCAGCGTGGTCTGTCTGCTGAACAATTTCTACCCTCGCGAAGCCAAAGTGCAGTGG AAGGTCGATAACGCTCTGCAGAGCGGCAACAGCCAGGAGTCTGTGACTGAACAGGACAGTAAAGATTCAACCTA TAGCCTGTCAAGCACACTGACTCTGAGCAAGGCAGACTACGAGAAGCACAAAGTGTATGCCTGCGAAGTCACAC ATCAGGGGCTGTCCTCTCCTGTGACTAAGAGCTTTAACAGAGGAGAGTGT
35	1811	VL	DIQMTQSPSSLSASVGDRVTITCKASQDVSIGVAWYQQKPGKAPKLLIYSASYRYTGVPSRFSGSGSGTDFTLT ISSLQPEDFATYYCQQYYIYPYTFGQGTKVEIK

SEQUENCE TABLE-continued

36	1811	VL	GATATTCAGATGACCCAGTCCCCAAGCTCCCTGAGTGCCTCAGTGGGCGACCGAGTCACCATCACATGCAAGGC TTCCCAGGATGTGTCTATTGGAGTCGCATGGTACCAGCAGAAGCCAGGCAAAGCACCCAAGCTGCTGATCTATA GCGCCTCCTACCGGTATACCGGCGTGCCCTCTAGATTCTCTGGCAGTGGGTCAGGAACAGACTTTACTCTGACC ATCTCTAGTCTGCAGCCTGAGGATTTCGCTACCTACTATTGCCAGCAGTACTATATCTACCCATATACCTTTGG CCAGGGGACAAAAGTGGAGATCAAG
37	1811	L1	QDVSIG
38	1811	L1	CAGGATGTGTCTATTGGA
39	1811	L3	QQYYIYPYT
40	1811	L3	CAGCAGTACTATATCTACCCATATACC
41	1811	L2	SAS
42	1811	L2	AGCGCCTCC
43	1811	CL	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTL SKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
44	1811	CL	AGGACTGTGGCCGCTCCCTCCGTCTTCATTTTTCCCCCTTCTGACGAACAGCTGAAAAGTGGCACAGCCAGCGT GGTCTGTCTGCTGAACAATTTCTACCCTCGCGAAGCCAAAGTGCAGTGGAAGGTCGATAACGCTCTGCAGAGCG GCAACAGCCAGGAGTCTGTGACTGAACAGGACAGTAAAGATTCAACCTATAGCCTGTCAAGCACACTGACTCTG AGCAAGGCAGACTACGAGAAGCACAAAGTGTATGCCTGCGAAGTCACACATCAGGGGCTGTCCTCTCCTGTGAC TAAGAGCTTTAACAGAGGAGAGTGT
45	5034	Full	DYKDDDDKDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSR SGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIKRTVAAPSVFIFPPSDERLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
46	5034	Full	GACTACAAAGACGACGATGACAAAGATATCCAGATGACCCAGTCCCCTAGCTCCCTGTCCGCTTCTGTGGGCGA TAGGGTCACTATTACCTGCCGCGCATCTCAGGACGTGAACACCGCAGTCGCCTGGTACCAGCAGAAGCCTGGGA AAGCTCCAAAGCTGCTGATCTACAGTGCATCATTCCTGTATTCAGGAGTGCCCAGCCGGTTTAGCGGCAGCAGA TCTGGCACCGATTTCACACTGACTATTTCTAGTCTGCAGCCTGAGGACTTTGCCACATACTATTGCCAGCAGCA CTATACCACACCCCCTACTTTCGGCCAGGGGACCAAAGTGGAGATCAAGCGAACTGTGGCCGCTCCAAGTGTCT TCATTTTTCCACCCAGCGATGAAAGACTGAAGTCCGGCACAGCTTCTGTGGTCTGTCTGCTGAACAATTTTTAC CCCAGAGAGGCCAAAGTGCAGTGGAAGGTCGACAACGCTCTGCAGAGTGGCAACAGCCAGGAGAGCGTGACAGA ACAGGATTCCAAAGACTCTACTTATAGTCTGTCAAGCACCCTGACACTGAGCAAGGCAGACTACGAAAAGCATA AAGTGTATGCCTGTGAGGTCACACATCAGGGGCTGTCATCACCAGTCACCAAATCATTCAATCGGGGGGAGTGC
47	5034	VL	DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLT ISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIK
48	5034	VL	GATATCCAGATGACCCAGTCCCCTAGCTCCCTGTCCGCTTCTGTGGGCGATAGGGTCACTATTACCTGCCGCGC ATCTCAGGACGTGAACACCGCAGTCGCCTGGTACCAGCAGAAGCCTGGGAAAGCTCCAAAGCTGCTGATCTACA GTGCATCATTCCTGTATTCAGGAGTGCCCAGCCGGTTTAGCGGCAGCAGATCTGGCACCGATTTCACACTGACT ATTTCTAGTCTGCAGCCTGAGGACTTTGCCACATACTATTGCCAGCAGCACTATACCACACCCCCTACTTTCGG CCAGGGGACCAAAGTGGAGATCAAG
49	5034	L1	QDVNTA
50	5034	L1	CAGGACGTGAACACCGCA
51	5034	L3	QQHYTTPPT
52	5034	L3	CAGCAGCACTATACCACACCCCCTACT
53	5034	L2	SAS
54	5034	L2	AGTGCATCA
55	5034	CL	RTVAAPSVFIFPPSDERLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTL SKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
56	5034	CL	CGAACTGTGGCCGCTCCAAGTGTCTTCATTTTTCCACCCAGCGATGAAAGACTGAAGTCCGGCACAGCTTCTGT GGTCTGTCTGCTGAACAATTTTTACCCCAGAGAGGCCAAAGTGCAGTGGAAGGTCGACAACGCTCTGCAGAGTG GCAACAGCCAGGAGAGCGTGACAGAACAGGATTCCAAAGACTCTACTTATAGTCTGTCAAGCACCCTGACACTG AGCAAGGCAGACTACGAAAAGCATAAAGTGTATGCCTGTGAGGTCACACATCAGGGGCTGTCATCACCAGTCAC CAAATCATTCAATCGGGGGGAGTGC
57	5037	Full	DYKDDDDKDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSR SGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIKRTVAAPSVFIFPPSDERLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSKESVTEQDSKDSTYSLSSRLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQUENCE TABLE-continued

58	5037	Full	GACTACAAAGACGACGATGACAAAGATATCCAGATGACCCAGTCCCCTAGCTCCCTGTCCGCTTCTGTGGGCGA TAGGGTCACTATTACCTGCCGCGCATCTCAGGACGTGAACACCGCAGTCGCCTGGTACCAGCAGAAGCCTGGGA AAGCTCCAAAGCTGCTGATCTACAGTGCATCATTCCTGTATTCAGGAGTGCCCAGCCGGTTTAGCGGCAGCAGA TCTGGCACCGATTTCACACTGACTATTTCTAGTCTGCAGCCTGAGGACTTTGCCACATACTATTGCCAGCAGCA CTATACCACACCCCCTACTTTCGGCCAGGGGACCAAAGTGGAGATCAAGCGAACTGTGGCCGCTCCAAGTGTCT TCATTTTTCCACCCAGCGATGAAAGACTGAAGTCCGGCACAGCTTCTGTGGTCTGTCTGCTGAACAATTTTTAC CCCAGAGAGGCCAAAGTGCAGTGGAAGGTCGACAACGCTCTGCAGAGTGGCAACAGCAAGGAGAGCGTGACAGA ACAGGATTCCAAAGACTCTACTTATAGTCTGTCAAGCAGACTGACACTGAGCAAGGCAGACTACGAAAAGCATA AAGTGTATGCCTGTGAGGTCACACATCAGGGGCTGTCATCACCAGTCACCAAATCATTCAATCGGGGGGAGTGC
59	5037	VL	DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLT ISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIK
60	5037	VL	GATATCCAGATGACCCAGTCCCCTAGCTCCCTGTCCGCTTCTGTGGGCGATAGGGTCACTATTACCTGCCGCGC ATCTCAGGACGTGAACACCGCAGTCGCCTGGTACCAGCAGAAGCCTGGGAAAGCTCCAAAGCTGCTGATCTACA GTGCATCATTCCTGTATTCAGGAGTGCCCAGCCGGTTTAGCGGCAGCAGATCTGGCACCGATTTCACACTGACT ATTTCTAGTCTGCAGCCTGAGGACTTTGCCACATACTATTGCCAGCAGCACTATACCACACCCCCTACTTTCGG CCAGGGGACCAAAGTGGAGATCAAG
61	5037	L1	QDVNTA
62	5037	L1	CAGGACGTGAACACCGCA
63	5037	L3	QQHYTTPPT
64	5037	L3	CAGCAGCACTATACCACACCCCCTACT
65	5037	L2	SAS
66	5037	L2	AGTGCATCA
67	5037	CL	RTVAAPSVFIFPPSDERLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSKESVTEQDSKDSTYSLSSRLTL SKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
68	5037	CL	CGAACTGTGGCCGCTCCAAGTGTCTTCATTTTTCCACCCAGCGATGAAAGACTGAAGTCCGGCACAGCTTCTGT GGTCTGTCTGCTGAACAATTTTTACCCCAGAGAGGCCAAAGTGCAGTGGAAGGTCGACAACGCTCTGCAGAGTG GCAACAGCAAGGAGAGCGTGACAGAACAGGATTCCAAAGACTCTACTTATAGTCTGTCAAGCAGACTGACACTG AGCAAGGCAGACTACGAAAAGCATAAAGTGTATGCCTGTGAGGTCACACATCAGGGGCTGTCATCACCAGTCAC CAAATCATTCAATCGGGGGGAGTGC
69	3382	Full	DIQMTQSPSSLSASVGDRVTITCKASQDVSIGVAWYQQKPGKAPKLLIYSASYRYTGVPSRFSGSGSGTDFTLT ISSLQPEDFATYYCQQYYIYPATFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQW KVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
70	3382	Full	GATATTCAGATGACCCAGTCCCCAAGCTCCCTGAGTGCCTCAGTGGGCGACCGAGTCACCATCACATGCAAGGC TTCCCAGGATGTGTCTATTGGAGTCGCATGGTACCAGCAGAAGCCAGGCAAAGCACCCAAGCTGCTGATCTATA GCGCCTCCTACCGGTATACCGGCGTGCCCTCTAGATTCTCTGGCAGTGGGTCAGGAACAGACTTTACTCTGACC ATCTCTAGTCTGCAGCCTGAGGATTTCGCTACCTACTATTGCCAGCAGTACTATATCTACCCAGCCACCTTTGG CCAGGGGACAAAAGTGGAGATCAAGAGGACTGTGGCCGCTCCCTCCGTCTTCATTTTTCCCCCTTCTGACGAAC AGCTGAAAAGTGGCACAGCCAGCGTGGTCTGTCTGCTGAACAATTTCTACCCTCGCGAAGCCAAAGTGCAGTGG AAGGTCGATAACGCTCTGCAGAGCGGCAACAGCCAGGAGTCTGTGACTGAACAGGACAGTAAAGATTCAACCTA TAGCCTGTCAAGCACACTGACTCTGAGCAAGGCAGACTACGAGAAGCACAAAGTGTATGCCTGCGAAGTCACAC ATCAGGGGCTGTCCTCTCCTGTGACTAAGAGCTTTAACAGAGGAGAGTGT
71	3382	VL	DIQMTQSPSSLSASVGDRVTITCKASQDVSIGVAWYQQKPGKAPKLLIYSASYRYTGVPSRFSGSGSGTDFTLT ISSLQPEDFATYYCQQYYIYPATFGQGTKVEIK
72	3382	VL	GATATTCAGATGACCCAGTCCCCAAGCTCCCTGAGTGCCTCAGTGGGCGACCGAGTCACCATCACATGCAAGGC TTCCCAGGATGTGTCTATTGGAGTCGCATGGTACCAGCAGAAGCCAGGCAAAGCACCCAAGCTGCTGATCTATA GCGCCTCCTACCGGTATACCGGCGTGCCCTCTAGATTCTCTGGCAGTGGGTCAGGAACAGACTTTACTCTGACC ATCTCTAGTCTGCAGCCTGAGGATTTCGCTACCTACTATTGCCAGCAGTACTATATCTACCCAGCCACCTTTGG CCAGGGGACAAAAGTGGAGATCAAG
73	3382	L1	QDVSIG
74	3382	L1	CAGGATGTGTCTATTGGA
75	3382	L3	QQYYIYPAT
76	3382	L3	CAGCAGTACTATATCTACCCAGCCACC
77	3382	L2	SAS
78	3382	L2	AGCGCCTCC

SEQUENCE TABLE-continued

79	3382	CL	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTL SKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
80	3382	CL	AGGACTGTGGCCGCTCCCTCCGTCTTCATTTTTCCCCCTTCTGACGAACAGCTGAAAAGTGGCACAGCCAGCGT GGTCTGTCTGCTGAACAATTTCTACCCTCGCGAAGCCAAAGTGCAGTGGAAGGTCGATAACGCTCTGCAGAGCG GCAACAGCCAGGAGTCTGTGACTGAACAGGACAGTAAAGATTCAACCTATAGCCTGTCAAGCACACTGACTCTG AGCAAGGCAGACTACGAGAAGCACAAAGTGTATGCCTGCGAAGTCACACATCAGGGGCTGTCCTCTCCTGTGAC TAAGAGCTTTAACAGAGGAGAGTGT
81	5065	Full	EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTISADT SKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCE VTDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKS CDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYVYPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFALVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL SLSPG
82	5065	Full	GAGGTGCAGCTGGTCGAAAGCGGAGGAGGACTGGTGCAGCCAGGAGGGTCACTGCGACTGAGCTGCGCAGCTTC CGGCTTCAACATCAAGGACACCTACATTCACTGGGTCCGCCAGGCTCCTGGAAAAGGCCTGGAGTGGGTGGCAC GAATCTATCCAACTAATGGATACACCCGGTATGCCGACTCCGTGAAGGGCCGGTTCACCATTTCTGCAGATACA AGTAAAAACACTGCCTACCTGCAGATGAACAGCCTGCGAGCCGAAGATACAGCCGTGTACTATTGCAGCCGATG GGGAGGCGACGGCTTCTACGCTATGGATTATTGGGGGCAGGGAACCCTGGTCACAGTGAGCTCCGCATCAACAA AGGGGCCTAGCGTGTTTCCACTGGCCCCCTCTAGTAAATCCACCTCTGGGGGAACAGCAGCCCTGGGATGTGAG GTGACCGACTACTTCCCAGAGCCCGTCACTGTGAGCTGGAACTCCGGCGCCCTGACATCTGGGGTCCATACTTT TCCTGCTGTGCTGCAGTCAAGCGGCCTGTACAGCCTGTCCTCTGTGGTCACTGTGCCAAGTTCAAGCCTGGGGA CTCAGACCTATATCTGCAACGTGAATCACAAGCCATCCAATACCAAAGTCGACAAGAAAGTGGAACCCAAGTCT TGTGATAAAACACATACTTGCCCCCCTTGTCCTGCACCAGAGCTGCTGGGAGGACCAAGCGTGTTCCTGTTTCC ACCCAAGCCTAAAGACACCCTGATGATTAGTAGGACTCCAGAAGTCACCTGCGTGGTCGTGGACGTGAGCCACG AGGACCCCGAAGTCAAGTTCAACTGGTACGTGGATGGCGTCGAGGTGCATAATGCCAAGACAAAACCCAGGGAG GAACAGTACAACTCCACTTATCGCGTCGTGTCTGTCCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAAGGA GTATAAGTGCAAAGTGAGCAATAAGGCTCTGCCCGCACCTATCGAGAAAACAATTTCCAAGGCTAAAGGGCAGC CTAGAGAACCACAGGTGTACGTGTACCCTCCATCTAGGGACGAGCTGACCAAGAACCAGGTCAGTCTGACATGT CTGGTGAAAGGGTTCTATCCCAGCGATATCGCAGTGGAGTGGGAATCCAATGGACAGCCTGAGAACAATTACAA GACCACACCCCCTGTGCTGGACTCTGATGGAAGTTTCGCCCTGGTGAGTAAGCTGACCGTCGATAAATCACGGT GGCAGCAGGGCAACGTGTTCAGCTGTTCAGTGATGCACGAAGCACTGCACAACCACTACACCCAGAAAAGCCTG TCCCTGTCCCCCGGC
83	5065	VH	EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTISADT SKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSS
84	5065	VH	GAGGTGCAGCTGGTCGAAAGCGGAGGAGGACTGGTGCAGCCAGGAGGGTCACTGCGACTGAGCTGCGCAGCTTC CGGCTTCAACATCAAGGACACCTACATTCACTGGGTCCGCCAGGCTCCTGGAAAAGGCCTGGAGTGGGTGGCAC GAATCTATCCAACTAATGGATACACCCGGTATGCCGACTCCGTGAAGGGCCGGTTCACCATTTCTGCAGATACA AGTAAAAACACTGCCTACCTGCAGATGAACAGCCTGCGAGCCGAAGATACAGCCGTGTACTATTGCAGCCGATG GGGAGGCGACGGCTTCTACGCTATGGATTATTGGGGGCAGGGAACCCTGGTCACAGTGAGCTCC
85	5065	H1	GFNIKDTY
86	5065	H1	GGCTTCAACATCAAGGACACCTAC
87	5065	H3	SRWGGDGFYAMDY
88	5065	H3	AGCCGATGGGGAGGCGACGGCTTCTACGCTATGGATTAT
89	5065	H2	IYPTNGYT
90	5065	H2	ATCTATCCAACTAATGGATACACC
91	5065	CH1	ASTKGPSVFPLAPSSKSTSGGTAALGCEVTDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHKPSNTKVDKKV
92	5065	CH1	GCATCAACAAAGGGGCCTAGCGTGTTTCCACTGGCCCCCTCTAGTAAATCCACCTCTGGGGGAACAGCAGCCCT GGGATGTGAGGTGACCGACTACTTCCCAGAGCCCGTCACTGTGAGCTGGAACTCCGGCGCCCTGACATCTGGGG TCCATACTTTTCCTGCTGTGCTGCAGTCAAGCGGCCTGTACAGCCTGTCCTCTGTGGTCACTGTGCCAAGTTCA AGCCTGGGGACTCAGACCTATATCTGCAACGTGAATCACAAGCCATCCAATACCAAAGTCGACAAGAAAGTG
93	5065	CH2	APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK
94	5065	CH2	GCACCAGAGCTGCTGGGAGGACCAAGCGTGTTCCTGTTTCCACCCAAGCCTAAAGACACCCTGATGATTAGTAG GACTCCAGAAGTCACCTGCGTGGTCGTGGACGTGAGCCACGAGGACCCCGAAGTCAAGTTCAACTGGTACGTGG ATGGCGTCGAGGTGCATAATGCCAAGACAAAACCCAGGGAGGAACAGTACAACTCCACTTATCGCGTCGTGTCT GTCCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAAGGAGTATAAGTGCAAAGTGAGCAATAAGGCTCTGCC CGCACCTATCGAGAAAACAATTTCCAAGGCTAAA

SEQUENCE TABLE-continued

95	5065	CH3	GQPREPQVYVYPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFALVSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
96	5065	CH3	GGGCAGCCTAGAGAACCACAGGTGTACGTGTACCCTCCATCTAGGGACGAGCTGACCAAGAACCAGGTCAGTCT GACATGTCTGGTGAAAGGGTTCTATCCCAGCGATATCGCAGTGGAGTGGGAATCCAATGGACAGCCTGAGAACA ATTACAAGACCACACCCCCTGTGCTGGACTCTGATGGAAGTTTCGCCCTGGTGAGTAAGCTGACCGTCGATAAA TCACGGTGGCAGCAGGGCAACGTGTTCAGCTGTTCAGTGATGCACGAAGCACTGCACAACCACTACACCCAGAA AAGCCTGTCCCTGTCCCCCGGC
97	6586	Full	EVQLVESGGGLVQPGGSLRLSCAASGFTFADYTMDWVRQAPGKGLEWVGDVNPNSGCSIYNQRFKGRFTFSVDR SKNTLYLQMNSLRAEDTAVYYCARNLGPSFYFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYVYPPSRDELTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFALVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
98	6586	Full	GAGGTGCAGCTGGTGGAATCAGGAGGGGGCCTGGTGCAGCCCGGAGGGTCTCTGCGACTGTCATGTGCCGCTTC TGGGTTCACTTTCGCAGACTACACAATGGATTGGGTGCGACAGGCCCCCGGAAAGGGACTGGAGTGGGTGGGCG ATGTCAACCCTAATTCTGGCGGGAGTATCTACAACCAGCGGTTCAAGGGGAGATTCACTTTTTCAGTGGACAGA AGCAAAAACACCCTGTATCTGCAGATGAACAGCCTGAGGGCCGAAGATACCGCTGTCTACTATTGCGCTCGCAA TCTGGGCCCCAGTTTCTACTTTGACTATTGGGGGCAGGGAACCCTGGTGACAGTCAGCTCCGCTAGCACTAAGG GGCCTTCCGTGTTTCCACTGGCTCCCTCTAGTAAATCCACCTCTGGAGGCACAGCTGCACTGGGATGTCTGGTG AAGGATTACTTCCCTGAACCAGTCACAGTGAGTTGGAACTCAGGGGCTCTGACAAGTGGAGTCCATACTTTTCC CGCAGTGCTGCAGTCAAGCGGACTGTACTCCCTGTCCTCTGTGGTCACCGTGCCTAGTTCAAGCCTGGGCACCC AGACATATATCTGCAACGTGAATCACAAGCCATCAAATACAAAAGTCGACAAGAAAGTGGAGCCCAAGAGCTGT GATAAAACTCATACCTGCCCACCTTGTCCGGCGCCAGAACTGCTGGGAGGACCAAGCGTGTTCCTGTTTCCACC CAAGCCTAAAGACACCCTGATGATTTCCCGGACTCCTGAGGTCACCTGCGTGGTCGTGGACGTGTCTCACGAGG ACCCCGAAGTCAAGTTCAACTGGTACGTGGATGGCGTCGAAGTGCATAATGCCAAGACCAAACCCCGGGAGGAA CAGTACAACTCTACCTATAGAGTCGTGAGTGTCCTGACAGTGCTGCACCAGGACTGGCTGAATGGGAAGGAGTA TAAGTGTAAAGTGAGCAACAAAGCCCTGCCCGCCCCAATCGAAAAAACAATCTCTAAAGCAAAAGGACAGCCTC GCGAACCACAGGTCTACGTCTACCCCCCATCAAGAGATGAACTGACAAAAAATCAGGTCTCTCTGACATGCCTG GTCAAAGGATTCTACCCTTCCGACATCGCCGTGGAGTGGGAAAGTAACGGCCAGCCCGAGAACAATTACAAGAC CACACCCCCTGTCCTGGACTCTGATGGGAGTTTCGCTCTGGTGTCAAAGCTGACCGTCGATAAAAGCCGGTGGC AGCAGGGCAATGTGTTTAGCTGCTCCGTCATGCACGAAGCCCTGCACAATCACTACACACAGAAGTCCCTGAGC CTGAGCCCTGGC
99	6586	VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFADYTMDWVRQAPGKGLEWVGDVNPNSGCSIYNQRFKGRFTFSVDR SKNTLYLQMNSLRAEDTAVYYCARNLGPSFYFDYWGQGTLVTVSS
100	6586	VH	GAGGTGCAGCTGGTGGAATCAGGAGGGGGCCTGGTGCAGCCCGGAGGGTCTCTGCGACTGTCATGTGCCGCTTC TGGGTTCACTTTCGCAGACTACACAATGGATTGGGTGCGACAGGCCCCCGGAAAGGGACTGGAGTGGGTGGGCG ATGTCAACCCTAATTCTGGCGGGAGTATCTACAACCAGCGGTTCAAGGGGAGATTCACTTTTTCAGTGGACAGA AGCAAAAACACCCTGTATCTGCAGATGAACAGCCTGAGGGCCGAAGATACCGCTGTCTACTATTGCGCTCGCAA TCTGGGCCCCAGTTTCTACTTTGACTATTGGGGGCAGGGAACCCTGGTGACAGTCAGCTCC
101	6586	H1	GFTFADYT
102	6586	H1	GGGTTCACTTTCGCAGACTACACA
103	6586	H3	ARNLGPSFYFDY
104	6586	H3	GCTCGCAATCTGGGCCCCAGTTTCTACTTTGACTAT
105	6586	H2	VNPNSGGS
106	6586	H2	GTCAACCCTAATTCTGGCGGGAGT
107	6586	CH1	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHKPSNTKVDKKV
108	6586	CH1	GCTAGCACTAAGGGGCCTTCCGTGTTTCCACTGGCTCCCTCTAGTAAATCCACCTCTGGAGGCACAGCTGCACT GGGATGTCTGGTGAAGGATTACTTCCCTGAACCAGTCACAGTGAGTTGGAACTCAGGGGCTCTGACAAGTGGAG TCCATACTTTTCCCGCAGTGCTGCAGTCAAGCGGACTGTACTCCCTGTCCTCTGTGGTCACCGTGCCTAGTTCA AGCCTGGGCACCCAGACATATATCTGCAACGTGAATCACAAGCCATCAAATACAAAAGTCGACAAGAAAGTG
109	6586	CH2	APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK
110	6586	CH2	GCGCCAGAACTGCTGGGAGGACCAAGCGTGTTCCTGTTTCCACCCAAGCCTAAAGACACCCTGATGATTTCCCG GACTCCTGAGGTCACCTGCGTGGTCGTGGACGTGTCTCACGAGGACCCCGAAGTCAAGTTCAACTGGTACGTGG ATGGCGTCGAAGTGCATAATGCCAAGACCAAACCCCGGGAGGAACAGTACAACTCTACCTATAGAGTCGTGAGT GTCCTGACAGTGCTGCACCAGGACTGGCTGAATGGGAAGGAGTATAAGTGTAAAGTGAGCAACAAAGCCCTGCC CGCCCCAATCGAAAAAACAATCTCTAAAGCAAAA

SEQUENCE TABLE-continued

111	6586	CH3	GQPREPQVYVYPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFALVSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
112	6586	CH3	GGACAGCCTCGCGAACCACAGGTCTACGTCTACCCCCCATCAAGAGATGAACTGACAAAAAATCAGGTCTCTCT GACATGCCTGGTCAAAGGATTCTACCCTTCCGACATCGCCGTGGAGTGGGAAAGTAACGGCCAGCCCGAGAACA ATTACAAGACCACACCCCCTGTCCTGGACTCTGATGGGAGTTTCGCTCTGGTGTCAAAGCTGACCGTCGATAAA AGCCGGTGGCAGCAGGGCAATGTGTTTAGCTGCTCCGTCATGCACGAAGCCCTGCACAATCACTACACACAGAA GTCCCTGAGCCTGAGCCCTGGC
113	3904	Full	YPYDVPDYATGSDIQMTQSPSSLSASVGDRVTITCKASQDVSIGVAWYQQKPGKAPKLLIYSASYRYTGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQYYIYPYTFGQGTKVEIKRTVAAPSVFIFPPSDEELKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSEESVTEQDSKDSTYSLSSTLELSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC
114	3904	Full	TATCCCTACGATGTGCCTGACTACGCTACTGGCTCCGATATCCAGATGACCCAGTCTCCAAGCTCCCTGAGTGC ATCAGTGGGGGACCGAGTCACCATCACATGCAAGGCTTCCCAGGATGTGTCTATTGGAGTCGCATGGTACCAGC AGAAGCCAGGCAAAGCACCCAAGCTGCTGATCTACAGCGCCTCCTACCGGTATACTGGGGTGCCTTCCAGATTC TCTGGCAGTGGGTCAGGAACCGACTTTACTCTGACCATCTCTAGTCTGCAGCCCGAGGATTTCGCCACCTACTA TTGCCAGCAGTACTATATCTACCCTTATACCTTTGGCCAGGGGACAAAAGTGGAGATCAAGAGGACAGTGGCCG CTCCAAGTGTCTTCATTTTTCCCCCTTCCGACGAAGAGCTGAAAAGTGGAACTGCTTCAGTGGTCTGTCTGCTG AACAATTTCTACCCCCGCGAAGCCAAAGTGCAGTGGAAGGTCGATAACGCTCTGCAGAGCGGCAATTCCGAGGA GTCTGTGACAGAACAGGACAGTAAAGATTCAACTTATAGCCTGTCAAGCACACTGGAGCTGTCTAAGGCAGACT ACGAGAAGCACAAAGTGTATGCCTGCGAAGTCACCCATCAGGGGCTGTCCTCTCCCGTGACAAAGAGCTTTAAC AGAGGAGAGTGT
115	3904	VL	DIQMTQSPSSLSASVGDRVTITCKASQDVSIGVAWYQQKPGKAPKLLIYSASYRYTGVPSRFSGSGSGTDFTLT ISSLQPEDFATYYCQQYYIYPYTFGQGTKVEIK
116	3904	VL	GATATCCAGATGACCCAGTCTCCAAGCTCCCTGAGTGCATCAGTGGGGGACCGAGTCACCATCACATGCAAGGC TTCCCAGGATGTGTCTATTGGAGTCGCATGGTACCAGCAGAAGCCAGGCAAAGCACCCAAGCTGCTGATCTACA GCGCCTCCTACCGGTATACTGGGGTGCCTTCCAGATTCTCTGGCAGTGGGTCAGGAACCGACTTTACTCTGACC ATCTCTAGTCTGCAGCCCGAGGATTTCGCCACCTACTATTGCCAGCAGTACTATATCTACCCTTATACCTTTGG CCAGGGGACAAAAGTGGAGATCAAG
117	3904	L1	QDVSIG
118	3904	L1	CAGGATGTGTCTATTGGA
119	3904	L3	QQYYIYPYT
120	3904	L3	CAGCAGTACTATATCTACCCTTATACC
121	3904	L2	SAS
122	3904	L2	AGCGCCTCC
123	3904	CL	RTVAAPSVFIFPPSDEELKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSEESVTEQDSKDSTYSLSSTLEL SKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
124	3904	CL	AGGACAGTGGCCGCTCCAAGTGTCTTCATTTTTCCCCCTTCCGACGAAGAGCTGAAAAGTGGAACTGCTTCAGT GGTCTGTCTGCTGAACAATTTCTACCCCCGCGAAGCCAAAGTGCAGTGGAAGGTCGATAACGCTCTGCAGAGCG GCAATTCCGAGGAGTCTGTGACAGAACAGGACAGTAAAGATTCAACTTATAGCCTGTCAAGCACACTGGAGCTG TCTAAGGCAGACTACGAGAAGCACAAAGTGTATGCCTGCGAAGTCACCCATCAGGGGCTGTCCTCTCCCGTGAC AAAGAGCTTTAACAGAGGAGAGTGT
125	4553	Full	EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTISADT SKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKS CDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYVYPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFALVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL SLSPGK
126	4553	Full	GAAGTCCAGCTGGTCGAAAGCGGAGGAGGACTGGTGCAGCCAGGAGGGTCTCTGCGACTGAGTTGCGCCGCTTC AGGCTTCAACATCAAGGACACCTACATTCACTGGGTGCGCCAGGCTCCTGGAAAAGGCCTGGAGTGGGTGGCAC GAATCTATCCAACTAATGGATACACCCGGTATGCAGACAGCGTGAAGGGCCGGTTCACCATTAGCGCAGATACA TCCAAAAACACTGCCTACCTGCAGATGAACAGCCTGCGAGCCGAAGATACTGCTGTGTACTATTGCAGTCGGTG GGGAGGCGACGGCTTCTACGCTATGGATTATTGGGGGCAGGGAACCCTGGTCACAGTGAGCTCCGCATCTACAA AGGGGCCTAGTGTGTTTCCACTGGCCCCCTCTAGTAAATCCACCTCTGGGGGAACAGCAGCCCTGGGATGTCTG GTGAAGGACTATTTCCCAGAGCCCGTCACTGTGAGTTGGAACTCAGGCGCCCTGACATCCGGGGTCCATACTTT TCCTGCTGTGCTGCAGTCAAGCGGCCTGTACTCTCTGTCCTCTGTGGTCACCGTGCCAAGTTCAAGCCTGGGGA CTCAGACCTATATCTGCAACGTGAATCACAAGCCAAGCAATACAAAAGTCGACAAGAAAGTGGAACCCAAGAGC TGTGATAAAACACATACTTGCCCCCCTTGTCCTGCACCAGAGCTGCTGGGAGGACCATCCGTGTTCCTGTTTCC ACCCAAGCCTAAAGACACCCTGATGATTTCCAGGACTCCAGAAGTCACCTGCGTGGTCGTGGACGTGTCTCACG AGGACCCCGAAGTCAAGTTCAACTGGTACGTGGATGGCGTCGAGGTGCATAATGCCAAGACAAAACCCAGGGAG GAACAGTACAACTCAACTTATCGCGTCGTGAGCGTCCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAAGGA

SEQUENCE TABLE-continued

			GTATAAGTGCAAAGTGAGCAATAAGGCTCTGCCCGCACCTATCGAGAAAACCATTAGCAAGGCCAAAGGGCAGC CTAGAGAACCACAGGTCTACGTGTATCCTCCAAGCAGGGACGAGCTGACCAAGAACCAGGTCTCCCTGACATGT CTGGTGAAAGGGTTTTACCCCAGTGATATCGCTGTGGAGTGGGAATCAAATGGACAGCCTGAAAACAATTATAA GACCACACCCCCTGTGCTGGACAGCGATGGCAGCTTCGCTCTGGTCTCCAAGCTGACTGTGGATAAATCTCGGT GGCAGCAGGGCAACGTCTTTAGTTGTTCAGTGATGCATGAGGCACTGCACAATCATTACACCCAGAAGAGCCTG TCCCTGTCTCCCGGCAAA
127	4553	VH	EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTISADT SKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSS
128	4553	VH	GAAGTCCAGCTGGTCGAAAGCGGAGGAGGACTGGTGCAGCCAGGAGGGTCTCTGCGACTGAGTTGCGCCGCTTC AGGCTTCAACATCAAGGACACCTACATTCACTGGGTGCGCCAGGCTCCTGGAAAAGGCCTGGAGTGGGTGGCAC GAATCTATCCAACTAATGGATACACCCGGTATGCAGACAGCGTGAAGGGCCGGTTCACCATTAGCGCAGATACA TCCAAAAACACTGCCTACCTGCAGATGAACAGCCTGCGAGCCGAAGATACTGCTGTGTACTATTGCAGTCGGTG GGGAGGCGACGGCTTCTACGCTATGGATTATTGGGGGCAGGGAACCCTGGTCACAGTGAGCTCC
129	4553	H1	GFNIKDTY
130	4553	H1	GGCTTCAACATCAAGGACACCTAC
131	4553	H3	SRWGGDGFYAMDY
132	4553	H3	AGTCGGTGGGGAGGCGACGGCTTCTACGCTATGGATTAT
133	4553	H2	IYPTNGYT
134	4553	H2	ATCTATCCAACTAATGGATACACC
135	4553	CH1	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHKPSNTKVDKKV
136	4553	CH1	GCATCTACAAAGGGGCCTAGTGTGTTTCCACTGGCCCCCTCTAGTAAATCCACCTCTGGGGGAACAGCAGCCCT GGGATGTCTGGTGAAGGACTATTTCCCAGAGCCCGTCACTGTGAGTTGGAACTCAGGCGCCCTGACATCCGGGG TCCATACTTTTCCTGCTGTGCTGCAGTCAAGCGGCCTGTACTCTCTGTCCTCTGTGGTCACCGTGCCAAGTTCA AGCCTGGGGACTCAGACCTATATCTGCAACGTGAATCACAAGCCAAGCAATACAAAAGTCGACAAGAAAGTG
137	4553	CH2	APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK
138	4553	CH2	GCACCAGAGCTGCTGGGAGGACCATCCGTGTTCCTGTTTCCACCCAAGCCTAAAGACACCCTGATGATTTCCAG GACTCCAGAAGTCACCTGCGTGGTCGTGGACGTGTCTCACGAGGACCCCGAAGTCAAGTTCAACTGGTACGTGG ATGGCGTCGAGGTGCATAATGCCAAGACAAAACCCAGGGAGGAACAGTACAACTCAACTTATCGCGTCGTGAGC GTCCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAAGGAGTATAAGTGCAAAGTGAGCAATAAGGCTCTGCC CGCACCTATCGAGAAAACCATTAGCAAGGCCAAA
139	4553	CH3	GQPREPQVYVYPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFALVSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
140	4553	CH3	GGGCAGCCTAGAGAACCACAGGTCTACGTGTATCCTCCAAGCAGGGACGAGCTGACCAAGAACCAGGTCTCCCT GACATGTCTGGTGAAAGGGTTTTACCCCAGTGATATCGCTGTGGAGTGGGAATCAAATGGACAGCCTGAAAACA ATTATAAGACCACACCCCCTGTGCTGGACAGCGATGGCAGCTTCGCTCTGGTCTCCAAGCTGACTGTGGATAAA TCTCGGTGGCAGCAGGGCAACGTCTTTAGTTGTTCAGTGATGCATGAGGCACTGCACAATCATTACACCCAGAA GAGCCTGTCCCTGTCTCCCGGC
141	716	Full	EPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLICLVKGFYPSDIAVEWESNGQPENRYMTWPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
142	716	Full	GAGCCCAAGAGCAGCGATAAGACCCACACCTGCCCTCCCTGTCCAGCTCCAGAACTGCTGGGAGGACCTAGCGT GTTCCTGTTTCCCCCTAAGCCAAAAGACACTCTGATGATTTCCAGGACTCCCGAGGTGACCTGCGTGGTGGTGG ACGTGTCTCACGAGGACCCCGAAGTGAAGTTCAACTGGTACGTGGATGGCGTGGAAGTGCATAATGCTAAGACA AAACCAAGAGAGGAACAGTACAACTCCACTTATCGCGTCGTGAGCGTGCTGACCGTGCTGCACCAGGACTGGCT GAACGGGAAGGAGTATAAGTGCAAAGTCAGTAATAAGGCCCTGCCTGCTCCAATCGAAAAAACCATCTCTAAGG CCAAAGGCCAGCCAAGGGAGCCCCAGGTGTACACACTGCCACCCAGCAGAGACGAACTGACCAAGAACCAGGTG TCCCTGATCTGTCTGGTGAAAGGCTTCTATCCTAGTGATATTGCTGTGGAGTGGGAATCAAATGGACAGCCAGA GAACAGATACATGACCTGGCCTCCAGTGCTGGACAGCGATGGCAGCTTCTTCCTGTATTCCAAGCTGACAGTGG ATAAATCTCGATGGCAGCAGGGGAACGTGTTTAGTTGTTCAGTGATGCATGAAGCCCTGCACAATCATTACACT CAGAAGAGCCTGTCCCTGTCTCCCGGCAAA
143	716	CH2	APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK
144	716	CH2	GCTCCAGAACTGCTGGGAGGACCTAGCGTGTTCCTGTTTCCCCCTAAGCCAAAAGACACTCTGATGATTTCCAG GACTCCCGAGGTGACCTGCGTGGTGGTGGACGTGTCTCACGAGGACCCCGAAGTGAAGTTCAACTGGTACGTGG ATGGCGTGGAAGTGCATAATGCTAAGACAAAACCAAGAGAGGAACAGTACAACTCCACTTATCGCGTCGTGAGC

SEQUENCE TABLE-continued

			GTGCTGACCGTGCTGCACCAGGACTGGCTGAACGGGAAGGAGTATAAGTGCAAAGTCAGTAATAAGGCCCTGCC TGCTCCAATCGAAAAAACCATCTCTAAGGCCAAA
145	716	CH3	GQPREPQVYTLPPSRDELTKNQVSLICLVKGFYPSDIAVEWESNGQPENRYMTWPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
146	716	CH3	GGCCAGCCAAGGGAGCCCCAGGTGTACACACTGCCACCCAGCAGAGACGAACTGACCAAGAACCAGGTGTCCCT GATCTGTCTGGTGAAAGGCTTCTATCCTAGTGATATTGCTGTGGAGTGGGAATCAAATGGACAGCCAGAGAACA GATACATGACCTGGCCTCCAGTGCTGGACAGCGATGGCAGCTTCTTCCTGTATTCCAAGCTGACAGTGGATAAA TCTCGATGGCAGCAGGGGAACGTGTTTAGTTGTTCAGTGATGCATGAAGCCCTGCACAATCATTACACTCAGAA GAGCCTGTCCCTGTCTCCCGGC
147	719	Full	DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLT ISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIKGGSGGGSGGGSGGGSGGGSGEVQLVESGGGLVQPGGSLRLS CAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYY CSRWGGDGFYAMDYWGQGTLVTVSSAAEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI SKAKGQPREPQVYTYPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDEDGSFALVSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPCK
148	719	Full	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGC AAGTCAGGACGTTAACACCGCTGTAGCTTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATT CTGCATCCTTTTTGTACAGTGGGGTCCCATCAAGGTTCAGTGGCAGTCGATCTGGGACAGATTTCACTCTCACC ATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGCATTACACTACCCCACCCACTTTCGG CCAAGGGACCAAAGTGGAGATCAAAGGTGGTTCTGGTGGTGGTTCTGGTGGTGGTTCTGGTGGTGGTTCTGGTG GTGGTTCTGGTGAAGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGCGGGTCCCTGAGACTCTCC TGTGCAGCCTCTGGATTCAACATTAAAGATACTTATATCCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTGGA GTGGGTCGCACGTATTTATCCCACAAATGGTTACACACGGTATGCGGACTCTGTGAAGGGCCGATTCACCATCT CCGCAGACACTTCCAAGAACACCGCGTATCTGCAAATGAACAGTCTGAGAGCTGAGGACACGGCCGTTTATTAC TGTTCAAGATGGGGCGGAGACGGTTTCTACGCTATGGACTACTGGGGCCAAGGGACCCTGGTCACCGTCTCCTC AGCCGCCGAGCCCAAGAGCAGCGATAAGACCCACACCTGCCCTCCCTGTCCAGCTCCAGAACTGCTGGGAGGAC CTAGCGTGTTCCTGTTTCCCCCTAAGCCAAAAGACACTCTGATGATTTCCAGGACTCCCGAGGTGACCTGCGTG GTGGTGGACGTGTCTCACGAGGACCCCGAAGTGAAGTTCAACTGGTACGTGGATGGCGTGGAAGTGCATAATGC TAAGACAAAACCAAGAGAGGAACAGTACAACTCCACTTATCGCGTCGTGAGCGTGCTGACCGTGCTGCACCAGG ACTGGCTGAACGGGAAGGAGTATAAGTGCAAAGTCAGTAATAAGGCCCTGCCTGCTCCAATCGAAAAAACCATC TCTAAGGCCAAAGGCCAGCCAAGGGAGCCCCAGGTGTACACATACCCACCCAGCAGAGACGAACTGACCAAGAA CCAGGTGTCCCTGACATGTCTGGTGAAAGGCTTCTATCCTAGTGATATTGCTGTGGAGTGGGAATCAAATGGAC AGCCAGAGAACAATTACAAGACCACACCTCCAGTGCTGGACGAGGATGGCAGCTTCGCCCTGGTGTCCAAGCTG ACAGTGGATAAATCTCGATGGCAGCAGGGGAACGTGTTTAGTTGTTCAGTGATGCATGAAGCCCTGCACAATCA TTACACTCAGAAGAGCCTGTCCCTGTCTCCCGGCAAA
149	719	VL	DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLT ISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIK
150	719	VL	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGC AAGTCAGGACGTTAACACCGCTGTAGCTTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATT CTGCATCCTTTTTGTACAGTGGGGTCCCATCAAGGTTCAGTGGCAGTCGATCTGGGACAGATTTCACTCTCACC ATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGCATTACACTACCCCACCCACTTTCGG CCAAGGGACCAAAGTGGAGATCAAA
151	719	L1	QDVNTA
152	719	L1	CAGGACGTTAACACCGCT
153	719	L3	QQHYTTPPT
154	719	L3	CAACAGCATTACACTACCCCACCCACT
155	719	L2	SAS
156	719	L2	TCTGCATCC
157	719	VH	EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTISADT SKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSS
158	719	VH	GAAGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGCGGGTCCCTGAGACTCTCCTGTGCAGCCTC TGGATTCAACATTAAAGATACTTATATCCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTGGAGTGGGTCGCAC GTATTTATCCCACAAATGGTTACACACGGTATGCGGACTCTGTGAAGGGCCGATTCACCATCTCCGCAGACACT TCCAAGAACACCGCGTATCTGCAAATGAACAGTCTGAGAGCTGAGGACACGGCCGTTTATTACTGTTCAAGATG GGGCGGAGACGGTTTCTACGCTATGGACTACTGGGGCCAAGGGACCCTGGTCACCGTCTCCTCA
159	719	H1	GFNIKDTY
160	719	H1	GGATTCAACATTAAAGATACTTAT
161	719	H3	SRWGGDGFYAMDY

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162	719	H3	TCAAGATGGGGCGGAGACGGTTTCTACGCTATGGACTAC
163	719	H2	IYPTNGYT
164	719	H2	ATTTATCCCACAAATGGTTACACA
165	719	CH2	APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK
166	719	CH2	GCTCCAGAACTGCTGGGAGGACCTAGCGTGTTCCTGTTTCCCCCTAAGCCAAAAGACACTCTGATGATTTCCAG GACTCCCGAGGTGACCTGCGTGGTGGTGGACGTGTCTCACGAGGACCCCGAAGTGAAGTTCAACTGGTACGTGG ATGGCGTGGAAGTGCATAATGCTAAGACAAAACCAAGAGAGGAACAGTACAACTCCACTTATCGCGTCGTGAGC GTGCTGACCGTGCTGCACCAGGACTGGCTGAACGGGAAGGAGTATAAGTGCAAAGTCAGTAATAAGGCCCTGCC TGCTCCAATCGAAAAAACCATCTCTAAGGCCAAA
167	719	CH3	GQPREPQVYTYPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDEDGSFALVSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
168	719	CH3	GGCCAGCCAAGGGAGCCCCAGGTGTACACATACCCACCCAGCAGAGACGAACTGACCAAGAACCAGGTGTCCCT GACATGTCTGGTGAAAGGCTTCTATCCTAGTGATATTGCTGTGGAGTGGGAATCAAATGGACAGCCAGAGAACA ATTACAAGACCACACCTCCAGTGCTGGACGAGGATGGCAGCTTCGCCCTGGTGTCCAAGCTGACAGTGGATAAA TCTCGATGGCAGCAGGGGAACGTGTTTAGTTGTTCAGTGATGCATGAAGCCCTGCACAATCATTACACTCAGAA GAGCCTGTCCCTGTCTCCCGGC
169	720	Full	DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLT ISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIKGGSGGGSGGGSGGGSGGGSGEVQLVESGGGLVQPGGSLRLS CAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYY CSRWGGDGFYAMDYWGQGTLVTVSSAAEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI SKAKGQPREPQVYTLPPSRDELTKNQVSLICLVKGFYPSDIAVEWESNGQPENRYMTWPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPCK
170	720	Full	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGC AAGTCAGGACGTTAACACCGCTGTAGCTTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATT CTGCATCCTTTTTTGTACAGTGGGGTCCCATCAAGGTTCAGTGGCAGTCGATCTGGGACAGATTTCACTCTCACC ATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGCATTACACTACCCCACCCACTTTCGG CCAAGGGACCAAAGTGGAGATCAAAGGTGGTTCTGGTGGTGGTTCTGGTGGTGGTTCTGGTGGTGGTTCTGGTG GTGGTTCTGGTGAAGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGCGGGTCCCTGAGACTCTCC TGTGCAGCCTCTGGATTCAACATTAAAGATACTTATATCCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTGGA GTGGGTCGCACGTATTTATCCCACAAATGGTTACACACGGTATGCGGACTCTGTGAAGGGCCGATTCACCATCT CCGCAGACACTTCCAAGAACACCGCGTATCTGCAAATGAACAGTCTGAGAGCTGAGGACACGGCCGTTTATTAC TGTTCAAGATGGGGCGGAGACGGTTTCTACGCTATGGACTACTGGGGCCAAGGGACCCTGGTCACCGTCTCCTC AGCCGCCGAGCCCAAGAGCAGCGATAAGACCCACACCTGCCCTCCCTGTCCAGCTCCAGAACTGCTGGGAGGAC CTAGCGTGTTCCTGTTTCCCCCTAAGCCAAAAGACACTCTGATGATTTCCAGGACTCCCGAGGTGACCTGCGTG GTGGTGGACGTGTCTCACGAGGACCCCGAAGTGAAGTTCAACTGGTACGTGGATGGCGTGGAAGTGCATAATGC TAAGACAAAACCAAGAGAGGAACAGTACAACTCCACTTATCGCGTCGTGAGCGTGCTGACCGTGCTGCACCAGG ACTGGCTGAACGGGAAGGAGTATAAGTGCAAAGTCAGTAATAAGGCCCTGCCTGCTCCAATCGAAAAAACCATC TCTAAGGCCAAAGGCCAGCCAAGGGAGCCCCAGGTGTACACACTGCCACCCAGCAGAGACGAACTGACCAAGAA CCAGGTGTCCCTGATCTGTCTGGTGAAAGGCTTCTATCCTAGTGATATTGCTGTGGAGTGGGAATCAAATGGAC AGCCAGAGAACAGATACATGACCTGGCCTCCAGTGCTGGACAGCGATGGCAGCTTCTTCCTGTATTCCAAGCTG ACAGTGGATAAATCTCGATGGCAGCAGGGGAACGTGTTTAGTTGTTCAGTGATGCATGAAGCCCTGCACAATCA TTACACTCAGAAGAGCCTGTCCCTGTCTCCCGGCAAA
171	720	VL	DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLT ISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIK
172	720	VL	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGC AAGTCAGGACGTTAACACCGCTGTAGCTTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATT CTGCATCCTTTTTGTACAGTGGGGTCCCATCAAGGTTCAGTGGCAGTCGATCTGGGACAGATTTCACTCTCACC ATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGCATTACACTACCCCACCCACTTTCGG CCAAGGGACCAAAGTGGAGATCAAA
173	720	L1	QDVNTA
174	720	L1	CAGGACGTTAACACCGCT
175	720	L3	QQHYTTPPT
176	720	L3	CAACAGCATTACACTACCCCACCCACT
177	720	L2	SAS
178	720	L2	TCTGCATCC
179	720 S	VH	EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTISADT SKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVS

SEQUENCE TABLE-continued

180	720	VH	GAAGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGCGGGTCCCTGAGACTCTCCTGTGCAGCCTC TGGATTCAACATTAAAGATACTTATATCCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTGGAGTGGGTCGCAC GTATTTATCCCACAAATGGTTACACACGGTATGCGGACTCTGTGAAGGGCCGATTCACCATCTCCGCAGACACT TCCAAGAACACCGCGTATCTGCAAATGAACAGTCTGAGAGCTGAGGACACGGCCGTTTATTACTGTTCAAGATG GGGCGGAGACGGTTTCTACGCTATGGACTACTGGGGCCAAGGGACCCTGGTCACCGTCTCCTCA
181	720	H1	GFNIKDTY
182	720	H1	GGATTCAACATTAAAGATACTTAT
183	720	H3	SRWGGDGFYAMDY
184	720	H3	TCAAGATGGGGCGGAGACGGTTTCTACGCTATGGACTAC
185	720	H2	IYPTNGYT
186	720	H2	ATTTATCCCACAAATGGTTACACA
187	720	CH2	APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK
188	720	CH2	GCTCCAGAACTGCTGGGAGGACCTAGCGTGTTCCTGTTTCCCCCTAAGCCAAAAGACACTCTGATGATTTCCAG GACTCCCGAGGTGACCTGCGTGGTGGTGGACGTGTCTCACGAGGACCCCGAAGTGAAGTTCAACTGGTACGTGG ATGGCGTGGAAGTGCATAATGCTAAGACAAAACCAAGAGAGGAACAGTACAACTCCACTTATCGCGTCGTGAGC GTGCTGACCGTGCTGCACCAGGACTGGCTGAACGGGAAGGAGTATAAGTGCAAAGTCAGTAATAAGGCCCTGCC TGCTCCAATCGAAAAAACCATCTCTAAGGCCAAA
189	720 PG	CH3	GQPREPQVYTLPPSRDELTKNQVSLICLVKGFYPSDIAVEWESNGQPENRYMTWPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLS
190	720	CH3	GGCCAGCCAAGGGAGCCCCAGGTGTACACACTGCCACCCAGCAGAGACGAACTGACCAAGAACCAGGTGTCCCT GATCTGTCTGGTGAAAGGCTTCTATCCTAGTGATATTGCTGTGGAGTGGGAATCAAATGGACAGCCAGAGAACA GATACATGACCTGGCCTCCAGTGCTGGACAGCGATGGCAGCTTCTTCCTGTATTCCAAGCTGACAGTGGATAAA TCTCGATGGCAGCAGGGGAACGTGTTTAGTTGTTCAGTGATGCATGAAGCCCTGCACAATCATTACACTCAGAA GAGCCTGTCCCTGTCTCCCGGC
191	4561	Full	DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLT ISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQW KVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
192	4561	Full	GATATTCAGATGACCCAGTCCCCTAGCTCCCTGTCCGCTTCTGTGGGCGACAGGGTCACTATCACCTGCCGCGC ATCTCAGGATGTGAACACCGCAGTCGCCTGGTACCAGCAGAAGCCTGGGAAAGCTCCAAAGCTGCTGATCTACA GTGCATCATTCCTGTATTCAGGAGTGCCCAGCCGGTTTAGCGGCAGCAGATCTGGCACCGACTTCACACTGACT ATCTCTAGTCTGCAGCCTGAGGATTTTGCCACATACTATTGCCAGCAGCACTATACCACACCCCCTACTTTCGG CCAGGGGACCAAAGTGGAGATCAAGCGAACTGTGGCCGCTCCAAGTGTCTTCATTTTTCCACCCAGCGACGAAC AGCTGAAATCCGGCACAGCTTCTGTGGTCTGTCTGCTGAACAACTTCTACCCCAGAGAGGCCAAAGTGCAGTGG AAGGTCGATAACGCTCTGCAGAGTGGCAACAGCCAGGAGAGCGTGACAGAACAGGACTCCAAAGATTCTACTTA TAGTCTGTCAAGCACCCTGACACTGAGCAAGGCAGACTACGAAAAGCATAAAGTGTATGCCTGTGAGGTGACCC ATCAGGGGCTGTCTTCTCCCGTGACCAAGTCTTTCAACCGAGGCGAATGT
193	4561	VL	DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLT ISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIK
194	4561	VL	GATATTCAGATGACCCAGTCCCCTAGCTCCCTGTCCGCTTCTGTGGGCGACAGGGTCACTATCACCTGCCGCGC ATCTCAGGATGTGAACACCGCAGTCGCCTGGTACCAGCAGAAGCCTGGGAAAGCTCCAAAGCTGCTGATCTACA GTGCATCATTCCTGTATTCAGGAGTGCCCAGCCGGTTTAGCGGCAGCAGATCTGGCACCGACTTCACACTGACT ATCTCTAGTCTGCAGCCTGAGGATTTTGCCACATACTATTGCCAGCAGCACTATACCACACCCCCTACTTTCGG CCAGGGGACCAAAGTGGAGATCAAG
195	4561	L1	QDVNTA
196	4561	L1	CAGGATGTGAACACCGCA
197	4561	L3	QQHYTTPPT
198	4561	L3	CAGCAGCACTATACCACACCCCCTACT
199	4561	L2	SAS
200	4561	L2	AGTGCATCA
201	4561	CL	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTL SKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
202	4561	CL	CGAACTGTGGCCGCTCCAAGTGTCTTCATTTTTCCACCCAGCGACGAACAGCTGAAATCCGGCACAGCTTCTGT GGTCTGTCTGCTGAACAACTTCTACCCCAGAGAGGCCAAAGTGCAGTGGAAGGTCGATAACGCTCTGCAGAGTG GCAACAGCCAGGAGAGCGTGACAGAACAGGACTCCAAAGATTCTACTTATAGTCTGTCAAGCACCCTGACACTG

SEQUENCE TABLE-continued

			AGCAAGGCAGACTACGAAAAGCATAAAGTGTATGCCTGTGAGGTGACCCATCAGGGGCTGTCTTCTCCCGTGAC CAAGTCTTTCAACCGAGGCGAATGT
203	3041	Full	EVQLVESGGGLVQPGGSLRLSCAASGFTFTDYTMDWVRQAPGKGLEWVADVNPNSGCSIYNQRFKGRFTLSVDR SKNTLYLQMNSLRAEDTAVYYCARNLGPSFYFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYVLPPSRDELTKNQVSLLCL VKGFYPSDIAVEWESNGQPENNYLTWPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
204	3041	Full	GAAGTGCAGCTGGTCGAATCTGGAGGAGGACTGGTGCAGCCAGGAGGGTCCCTGCGCCTGTCTTGCGCCGCTAG TGGCTTCACTTTTACCGACTACACCATGGATTGGGTGCGACAGGCACCTGGAAAGGGCCTGGAGTGGGTCGCCG ATGTGAACCCAAATAGCGGAGGCTCCATCTACAACCAGCGGTTCAAGGGCCGGTTCACCCTGTCAGTGGACCGG AGCAAAAACACCCTGTATCTGCAGATGAATAGCCTGCGAGCCGAAGATACTGCTGTGTACTATTGCGCCCGGAA TCTGGGGCCCTCCTTCTACTTTGACTATTGGGGGCAGGGAACTCTGGTCACCGTGAGCTCCGCCTCCACCAAGG GACCTTCTGTGTTCCCACTGGCTCCCTCTAGTAAATCCACATCTGGGGGAACTGCAGCCCTGGGCTGTCTGGTG AAGGACTACTTCCCAGAGCCCGTCACAGTGTCTTGGAACAGTGGCGCTCTGACTTCTGGGGTCCACACCTTTCC TGCAGTGCTGCAGTCAAGCGGGCTGTACAGCCTGTCCTCTGTGGTCACCGTGCCAAGTTCAAGCCTGGGAACAC AGACTTATATCTGCAACGTGAATCACAAGCCATCCAATACAAAAGTCGACAAGAAAGTGGAACCCAAGTCTTGT GATAAAACCCATACATGCCCCCCTTGTCCTGCACCAGAGCTGCTGGGAGGACCAAGCGTGTTCCTGTTTCCACC CAAGCCTAAAGATACACTGATGATTAGTAGGACCCCAGAAGTCACATGCGTGGTCGTGGACGTGAGCCACGAGG ACCCCGAAGTCAAGTTTAACTGGTACGTGGACGGCGTCGAGGTGCATAATGCCAAGACTAAACCCAGGGAGGAA CAGTACAACAGTACCTATCGCGTCGTGTCAGTCCTGACAGTGCTGCATCAGGATTGGCTGAACGGGAAAGAGTA TAAGTGCAAAGTGAGCAATAAGGCTCTGCCCGCACCTATCGAGAAAACAATTTCCAAGGCAAAAGGACAGCCTA GAGAACCACAGGTGTACGTGCTGCCTCCATCAAGGGATGAGCTGACAAAGAACCAGGTCAGCCTGCTGTGTCTG GTGAAAGGATTCTATCCCTCTGACATTGCTGTGGAGTGGGAAAGTAATGGCCAGCCTGAGAACAATTACCTGAC CTGGCCCCCTGTGCTGGACTCAGATGGCAGCTTCTTTCTGTATAGCAAGCTGACCGTCGACAAATCCCGGTGGC AGCAGGGGAATGTGTTTAGTTGTTCAGTCATGCACGAGGCACTGCACAACCATTACACCCAGAAGTCACTGTCA CTGTCACCAGGG
205	3041	VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFTDYTMDWVRQAPGKGLEWVADVNPNSGCSIYNQRFKGRFTLSVDR SKNTLYLQMNSLRAEDTAVYYCARNLGPSFYFDYWGQGTLVTVSS
206	3041	VH	GAAGTGCAGCTGGTCGAATCTGGAGGAGGACTGGTGCAGCCAGGAGGGTCCCTGCGCCTGTCTTGCGCCGCTAG TGGCTTCACTTTTACCGACTACACCATGGATTGGGTGCGACAGGCACCTGGAAAGGGCCTGGAGTGGGTCGCCG ATGTGAACCCAAATAGCGGAGGCTCCATCTACAACCAGCGGTTCAAGGGCCGGTTCACCCTGTCAGTGGACCGG AGCAAAAACACCCTGTATCTGCAGATGAATAGCCTGCGAGCCGAAGATACTGCTGTGTACTATTGCGCCCGGAA TCTGGGGCCCTCCTTCTACTTTGACTATTGGGGGCAGGGAACTCTGGTCACCGTGAGCTCC
207	3041	H1	GFTFTDYT
208	3041	H1	GGCTTCACTTTTACCGACTACACC
209	3041	H3	ARNLGPSFYFDY
210	3041	H3	GCCCGGAATCTGGGGCCCTCCTTCTACTTTGACTAT
211	3041	H2	VNPNSGGS
212	3041	H2	GTGAACCCAAATAGCGGAGGCTCC
213	3041	CH1	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHKPSNTKVDKKV
214	3041	CH1	GCCTCCACCAAGGGACCTTCTGTGTTCCCACTGGCTCCCTCTAGTAAATCCACATCTGGGGGAACTGCAGCCCT GGGCTGTCTGGTGAAGGACTACTTCCCAGAGCCCGTCACAGTGTCTTGGAACAGTGGCGCTCTGACTTCTGGGG TCCACACCTTTCCTGCAGTGCTGCAGTCAAGCGGGCTGTACAGCCTGTCCTCTGTGGTCACCGTGCCAAGTTCA AGCCTGGGAACACAGACTTATATCTGCAACGTGAATCACAAGCCATCCAATACAAAAGTCGACAAGAAAGTG
215	3041	CH2	APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK
216	3041	CH2	GCACCAGAGCTGCTGGGAGGACCAAGCGTGTTCCTGTTTCCACCCAAGCCTAAAGATACACTGATGATTAGTAG GACCCCAGAAGTCACATGCGTGGTCGTGGACGTGAGCCACGAGGACCCCGAAGTCAAGTTTAACTGGTACGTGG ACGGCGTCGAGGTGCATAATGCCAAGACTAAACCCAGGGAGGAACAGTACAACAGTACCTATCGCGTCGTGTCA GTCCTGACAGTGCTGCATCAGGATTGGCTGAACGGGAAAGAGTATAAGTGCAAAGTGAGCAATAAGGCTCTGCC CGCACCTATCGAGAAAACAATTTCCAAGGCAAAA
217	3041	CH3	GQPREPQVYVLPPSRDELTKNQVSLLCLVKGFYPSDIAVEWESNGQPENNYLTWPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
218	3041	CH3	GGACAGCCTAGAGAACCACAGGTGTACGTGCTGCCTCCATCAAGGGATGAGCTGACAAAGAACCAGGTCAGCCT GCTGTGTCTGGTGAAAGGATTCTATCCCTCTGACATTGCTGTGGAGTGGGAAAGTAATGGCCAGCCTGAGAACA ATTACCTGACCTGGCCCCCTGTGCTGGACTCAGATGGCAGCTTCTTTCTGTATAGCAAGCTGACCGTCGACAAA TCCCGGTGGCAGCAGGGGAATGTGTTTAGTTGTTCAGTCATGCACGAGGCACTGCACAACCATTACACCCAGAA GTCACTGTCACTGTCACCAGGG

SEQUENCE TABLE-continued

219	3057	Full	EVQLVESGGGLVQPGGSLRLSCAASGFTFTDYTMDWVRQAPGKGLEWVADVNPNSGCSIYNQRFKGRFTLSVDR SKNTLYLQMNSLRAEDTAVYYCARNLGPSFYFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPELLGGPSVFLFPPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYVYPPSRDELTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFALVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
220	3057	Full	GAAGTGCAGCTGGTCGAATCTGGAGGAGGACTGGTGCAGCCAGGAGGGTCCCTGCGCCTGTCTTGCGCCGCTAG TGGCTTCACTTTTACCGACTACACCATGGATTGGGTGCGACAGGCACCTGGAAAGGGCCTGGAGTGGGTCGCCG ATGTGAACCCAAATAGCGGAGGCTCCATCTACAACCAGCGGTTCAAGGGCCGGTTCACCCTGTCAGTGGACCGG AGCAAAAACACCCTGTATCTGCAGATGAATAGCCTGCGAGCCGAAGATACTGCTGTGTACTATTGCGCCCGGAA TCTGGGGCCCTCCTTCTACTTTGACTATTGGGGGCAGGGAACTCTGGTCACCGTGAGCTCCGCCTCCACCAAGG GACCTTCTGTGTTCCCACTGGCTCCCTCTAGTAAATCCACATCTGGGGGAACTGCAGCCCTGGGCTGTCTGGTG AAGGACTACTTCCCAGAGCCCGTCACAGTGTCTTGGAACAGTGGCGCTCTGACTTCTGGGGTCCACACCTTTCC TGCAGTGCTGCAGTCAAGCGGGCTGTACAGCCTGTCCTCTGTGGTCACCGTGCCAAGTTCAAGCCTGGGAACAC AGACTTATATCTGCAACGTGAATCACAAGCCATCCAATACAAAAGTCGACAAGAAAGTGGAACCCAAGTCTTGT GATAAAACCCATACATGCCCCCCTTGTCCTGCACCAGAGCTGCTGGGAGGACCAAGCGTGTTCCTGTTTCCACC CAAGCCTAAAGATACACTGATGATTAGTAGGACCCCAGAAGTCACATGCGTGGTCGTGGACGTGAGCCACGAGG ACCCCGAAGTCAAGTTTAACTGGTACGTGGACGGCGTCGAGGTGCATAATGCCAAGACTAAACCCAGGGAGGAA CAGTACAACAGTACCTATCGCGTCGTGTCAGTCCTGACAGTGCTGCATCAGGATTGGCTGAACGGGAAAGAGTA TAAGTGCAAAGTGAGCAATAAGGCTCTGCCCGCACCTATCGAGAAAACAATTTCCAAGGCAAAAGGACAGCCTA GAGAACCACAGGTGTACGTGTATCCTCCATCAAGGGATGAGCTGACAAAGAACCAGGTCAGCCTGACTTGTCTG GTGAAAGGATTCTATCCCTCTGACATTGCTGTGGAGTGGGAAAGTAATGGCCAGCCTGAGAACAATTACAAGAC CACACCCCCTGTGCTGGACTCAGATGGCAGCTTCGCGCTGGTGAGCAAGCTGACCGTCGACAAATCCCGGTGGC AGCAGGGGAATGTGTTTAGTTGTTCAGTCATGCACGAGGCACTGCACAACCATTACACCCAGAAGTCACTGTCA CTGTCACCAGGG
221	3057	VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFTDYTMDWVRQAPGKGLEWVADVNPNSGCSIYNQRFKGRFTLSVDR SKNTLYLQMNSLRAEDTAVYYCARNLGPSFYFDYWGQGTLVTVSS
222	3057	VH	GAAGTGCAGCTGGTCGAATCTGGAGGAGGACTGGTGCAGCCAGGAGGGTCCCTGCGCCTGTCTTGCGCCGCTAG TGGCTTCACTTTTACCGACTACACCATGGATTGGGTGCGACAGGCACCTGGAAAGGGCCTGGAGTGGGTCGCCG ATGTGAACCCAAATAGCGGAGGCTCCATCTACAACCAGCGGTTCAAGGGCCGGTTCACCCTGTCAGTGGACCGG AGCAAAAACACCCTGTATCTGCAGATGAATAGCCTGCGAGCCGAAGATACTGCTGTGTACTATTGCGCCCGGAA TCTGGGGCCCTCCTTCTACTTTGACTATTGGGGGCAGGGAACTCTGGTCACCGTGAGCTCC
223	3057	H1	GFTFTDYT
224	3057	H1	GGCTTCACTTTTACCGACTACACC
225	3057	H3	ARNLGPSFYFDY
226	3057	H3	GCCCGGAATCTGGGGCCCTCCTTCTACTTTGACTAT
227	3057	H2	VNPNSGGS
228	3057	H2	GTGAACCCAAATAGCGGAGGCTCC
229	3057	CH1	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHKPSNTKVDKKV
230	3057	CH1	GCCTCCACCAAGGGACCTTCTGTGTTCCCACTGGCTCCCTCTAGTAAATCCACATCTGGGGGAACTGCAGCCCT GGGCTGTCTGGTGAAGGACTACTTCCCAGAGCCCGTCACAGTGTCTTGGAACAGTGGCGCTCTGACTTCTGGGG TCCACACCTTTCCTGCAGTGCTGCAGTCAAGCGGGCTGTACAGCCTGTCCTCTGTGGTCACCGTGCCAAGTTCA AGCCTGGGAACACAGACTTATATCTGCAACGTGAATCACAAGCCATCCAATACAAAAGTCGACAAGAAAGTG
231	3057	CH2	APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK
232	3057	CH2	GCACCAGAGCTGCTGGGAGGACCAAGCGTGTTCCTGTTTCCACCCAAGCCTAAAGATACACTGATGATTAGTAG GACCCCAGAAGTCACATGCGTGGTCGTGGACGTGAGCCACGAGGACCCCGAAGTCAAGTTTAACTGGTACGTGG ACGGCGTCGAGGTGCATAATGCCAAGACTAAACCCAGGGAGGAACAGTACAACAGTACCTATCGCGTCGTGTCA GTCCTGACAGTGCTGCATCAGGATTGGCTGAACGGGAAAGAGTATAAGTGCAAAGTGAGCAATAAGGCTCTGCC CGCACCTATCGAGAAAACAATTTCCAAGGCAAAA
233	3057	CH3	GQPREPQVYVYPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFALVSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
234	3057	CH3	GGACAGCCTAGAGAACCACAGGTGTACGTGTATCCTCCATCAAGGGATGAGCTGACAAAGAACCAGGTCAGCCT GACTTGTCTGGTGAAAGGATTCTATCCCTCTGACATTGCTGTGGAGTGGGAAAGTAATGGCCAGCCTGAGAACA ATTACAAGACCACACCCCCTGTGCTGGACTCAGATGGCAGCTTCGCGCTGGTGAGCAAGCTGACCGTCGACAAA TCCCGGTGGCAGCAGGGGAATGTGTTTAGTTGTTCAGTCATGCACGAGGCACTGCACAACCATTACACCCAGAA GTCACTGTCACTGTCACCAGGG

SEQUENCE TABLE-continued

235	1011	Full	EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTISADT SKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKS CDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYVYPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFALVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL SLSPGK
236	1011	Full	GAGGTGCAGCTGGTGGAAAGCGGAGGAGGACTGGTGCAGCCAGGAGGATCTCTGCGACTGAGTTGCGCCGCTTC AGGATTCAACATCAAGGACACCTACATTCACTGGGTGCGACAGGCTCCAGGAAAAGGACTGGAGTGGGTGGCTC GAATCTATCCCACTAATGGATACACCCGGTATGCCGACTCCGTGAAGGGGAGGTTTACTATTAGCGCCGATACA TCCAAAAACACTGCTTACCTGCAGATGAACAGCCTGCGAGCCGAAGATACCGCTGTGTACTATTGCAGTCGATG GGGAGGAGACGGATTCTACGCTATGGATTATTGGGGACAGGGGACCCTGGTGACAGTGAGCTCCGCCTCTACCA AGGGCCCCAGTGTGTTTCCCCTGGCTCCTTCTAGTAAATCCACCTCTGGAGGGACAGCCGCTCTGGGATGTCTG GTGAAGGACTATTTCCCCGAGCCTGTGACCGTGAGTTGGAACTCAGGCGCCCTGACAAGCGGAGTGCACACTTT TCCTGCTGTGCTGCAGTCAAGCGGGCTGTACTCCCTGTCCTCTGTGGTGACAGTGCCAAGTTCAAGCCTGGGCA CACAGACTTATATCTGCAACGTGAATCATAAGCCCTCAAATACAAAAGTGGACAAGAAAGTGGAGCCCAAGAGC TGTGATAAGACCCACACCTGCCCTCCCTGTCCAGCTCCAGAACTGCTGGGAGGACCTAGCGTGTTCCTGTTTCC CCCTAAGCCAAAAGACACTCTGATGATTTCCAGGACTCCCGAGGTGACCTGCGTGGTGGTGGACGTGTCTCACG AGGACCCCGAAGTGAAGTTCAACTGGTACGTGGATGGCGTGGAAGTGCATAATGCTAAGACAAAACCAAGAGAG GAACAGTACAACTCCACTTATCGCGTCGTGAGCGTGCTGACCGTGCTGCACCAGGACTGGCTGAACGGGAAGGA GTATAAGTGCAAAGTCAGTAATAAGGCCCTGCCTGCTCCAATCGAAAAAACCATCTCTAAGGCCAAAGGCCAGC CAAGGGAGCCCCAGGTGTACGTGTACCCACCCAGCAGAGACGAACTGACCAAGAACCAGGTGTCCCTGACATGT CTGGTGAAAGGCTTCTATCCTAGTGATATTGCTGTGGAGTGGGAATCAAATGGACAGCCAGAGAACAATTACAA GACCACACCTCCAGTGCTGGACAGCGATGGCAGCTTCGCCCTGGTGTCCAAGCTGACAGTGGATAAATCTCGAT GGCAGCAGGGGAACGTGTTTAGTTGTTCAGTGATGCATGAAGCCCTGCACAATCATTACACTCAGAAGAGCCTG TCCCTGTCTCCCGGCAAA
237	1011	VH	EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTISADT SKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSS
238	1011	VH	GAGGTGCAGCTGGTGGAAAGCGGAGGAGGACTGGTGCAGCCAGGAGGATCTCTGCGACTGAGTTGCGCCGCTTC AGGATTCAACATCAAGGACACCTACATTCACTGGGTGCGACAGGCTCCAGGAAAAGGACTGGAGTGGGTGGCTC GAATCTATCCCACTAATGGATACACCCGGTATGCCGACTCCGTGAAGGGGAGGTTTACTATTAGCGCCGATACA TCCAAAAACACTGCTTACCTGCAGATGAACAGCCTGCGAGCCGAAGATACCGCTGTGTACTATTGCAGTCGATG GGGAGGAGACGGATTCTACGCTATGGATTATTGGGGACAGGGGACCCTGGTGACAGTGAGCTCC
239	1011	H1	GFNIKDTY
240	1011	H1	GGATTCAACATCAAGGACACCTAC
241	1011	H3	SRWGGDGFYAMDY
242	1011	H3	AGTCGATGGGGAGGAGACGGATTCTACGCTATGGATTAT
243	1011	H2	IYPTNGYT
244	1011	H2	ATCTATCCCACTAATGGATACACC
245	1011	CH1	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHKPSNTKVDKKV
246	1011	CH1	GCCTCTACCAAGGGCCCCAGTGTGTTTCCCCTGGCTCCTTCTAGTAAATCCACCTCTGGAGGGACAGCCGCTCT GGGATGTCTGGTGAAGGACTATTTCCCCGAGCCTGTGACCGTGAGTTGGAACTCAGGCGCCCTGACAAGCGGAG TGCACACTTTTCCTGCTGTGCTGCAGTCAAGCGGGCTGTACTCCCTGTCCTCTGTGGTGACAGTGCCAAGTTCA AGCCTGGGCACACAGACTTATATCTGCAACGTGAATCATAAGCCCTCAAATACAAAAGTGGACAAGAAAGTG
247	1011	CH2	APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK
248	1011	CH2	GCTCCAGAACTGCTGGGAGGACCTAGCGTGTTCCTGTTTCCCCCTAAGCCAAAAGACACTCTGATGATTTCCAG GACTCCCGAGGTGACCTGCGTGGTGGTGGACGTGTCTCACGAGGACCCCGAAGTGAAGTTCAACTGGTACGTGG ATGGCGTGGAAGTGCATAATGCTAAGACAAAACCAAGAGAGGAACAGTACAACTCCACTTATCGCGTCGTGAGC GTGCTGACCGTGCTGCACCAGGACTGGCTGAACGGGAAGGAGTATAAGTGCAAAGTCAGTAATAAGGCCCTGCC TGCTCCAATCGAAAAAACCATCTCTAAGGCCAAA
249	1011	CH3	GQPREPQVYVYPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFALVSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
250	1011	CH3	GGCCAGCCAAGGGAGCCCCAGGTGTACGTGTACCCACCCAGCAGAGACGAACTGACCAAGAACCAGGTGTCCCT GACATGTCTGGTGAAAGGCTTCTATCCTAGTGATATTGCTGTGGAGTGGGAATCAAATGGACAGCCAGAGAACA ATTACAAGACCACACCTCCAGTGCTGGACAGCGATGGCAGCTTCGCCCTGGTGTCCAAGCTGACAGTGGATAAA TCTCGATGGCAGCAGGGGAACGTGTTTAGTTGTTCAGTGATGCATGAAGCCCTGCACAATCATTACACTCAGAA GAGCCTGTCCCTGTCTCCCGGC

SEQUENCE TABLE-continued

251	4560	Full	EPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYVLPPSRDELTKNQV SLLCLVKGFYPSDIAVEWESNGQPENNYLTWPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
252	4560	Full	GAACCTAAAAGCAGCGACAAGACCCACACATGCCCCCCTTGTCCAGCTCCAGAACTGCTGGGAGGACCAAGCGT GTTCCTGTTTCCACCCAAGCCCAAAGATACACTGATGATCAGCCGAACTCCCGAGGTCACCTGCGTGGTCGTGG ACGTGTCCCACGAGGACCCCGAAGTCAAGTTCAACTGGTACGTGGACGGCGTCGAAGTGCATAATGCAAAGACT AAACCACGGGAGGAACAGTACAACTCTACATATAGAGTCGTGAGTGTCCTGACTGTGCTGCATCAGGATTGGCT GAACGGCAAAGAGTATAAGTGCAAAGTGTCTAATAAGGCCCTGCCTGCTCCAATCGAGAAAACTATTAGTAAGG CAAAAGGGCAGCCCAGGGAACCTCAGGTCTACGTGCTGCCTCCAAGTCGCGACGAGCTGACCAAGAACCAGGTC TCACTGCTGTGTCTGGTGAAAGGATTCTATCCTTCCGATATTGCCGTGGAGTGGGAATCTAATGGCCAGCCAGA GAACAATTACCTGACCTGGCCCCCTGTGCTGGACAGCGATGGGTCCTTCTTTCTGTATTCAAAGCTGACAGTGG ACAAAAGCAGATGGCAGCAGGGAAACGTCTTTAGCTGTTCCGTGATGCACGAAGCCCTGCACAATCATTACACC CAGAAGTCTCTGAGTCTGTCACCTGGCAAA
253	4560	CH2	APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK
254	4560	CH2	GCTCCAGAACTGCTGGGAGGACCAAGCGTGTTCCTGTTTCCACCCAAGCCCAAAGATACACTGATGATCAGCCG AACTCCCGAGGTCACCTGCGTGGTCGTGGACGTGTCCCACGAGGACCCCGAAGTCAAGTTCAACTGGTACGTGG ACGGCGTCGAAGTGCATAATGCAAAGACTAAACCACGGGAGGAACAGTACAACTCTACATATAGAGTCGTGAGT GTCCTGACTGTGCTGCATCAGGATTGGCTGAACGGCAAAGAGTATAAGTGCAAAGTGTCTAATAAGGCCCTGCC TGCTCCAATCGAGAAAACTATTAGTAAGGCAAAA
255	4560	CH3	GQPREPQVYVLPPSRDELTKNQVSLLCLVKGFYPSDIAVEWESNGQPENNYLTWPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
256	4560	CH3	GGGCAGCCCAGGGAACCTCAGGTCTACGTGCTGCCTCCAAGTCGCGACGAGCTGACCAAGAACCAGGTCTCACT GCTGTGTCTGGTGAAAGGATTCTATCCTTCCGATATTGCCGTGGAGTGGGAATCTAATGGCCAGCCAGAGAACA ATTACCTGACCTGGCCCCCTGTGCTGGACAGCGATGGGTCCTTCTTTCTGTATTCAAAGCTGACAGTGGACAAA AGCAGATGGCAGCAGGGAAACGTCTTTAGCTGTTCCGTGATGCACGAAGCCCTGCACAATCATTACACCCAGAA GTCTCTGAGTCTGTCACCTGGC
257	3317	Full	DIQMTQSPSSLSASVGDRVTITCKASQDVSIGVAWYQQKPGKAPKLLIYSASYRYTGVPSRFSGSGSGTDFTLT ISSLQPEDFATYYCQQYYIYPYTFGQGTKVEIKGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASG FTFTDYTMDWVRQAPGKGLEWVADVNPNSGCSIYNQRFKGRFTLSVDRSKNTLYLQMNSLRAEDTAVYYCARNL GPSFYFDYWGQGTLVTVSSAAEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQ PREPQVYVYPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFALVSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPCK
258	3317	Full	GACATTCAGATGACCCAGAGCCCTAGCTCCCTGAGTGCCTCAGTCGGGGACAGGGTGACTATCACCTGCAAGGC TTCACAGGATGTCAGCATTGGCGTGGCATGGTACCAGCAGAAGCCAGGGAAAGCACCCAAGCTGCTGATCTATA GCGCCTCCTACAGGTATACAGGCGTGCCATCCCGCTTCTCTGGCAGTGGGTCAGGAACTGACTTTACACTGACT ATTTCTAGTCTGCAGCCCGAAGATTTCGCCACATACTATTGCCAGCAGTACTATATCTACCCTTATACTTTTGG CCAGGGGACCAAAGTGGAGATTAAGGGCGGAGGAGGCTCCGGAGGAGGAGGGGTCTGGAGGAGGAGGAAGTGAGG TCCAGCTGGTGGAATCTGGAGGAGGACTGGTGCAGCCAGGAGGGTCCCTGAGGCTGTCTTGTGCCGCTAGTGGC TTCACCTTTACAGACTACACAATGGATTGGGTGCGCCAGGCACCAGGAAAGGGACTGGAATGGGTCGCTGATGT GAACCCTAATAGCGGAGGCTCCATCTACAACCAGCGGTTCAAAGGACGGTTCACCCTGTCAGTGGACCGGAGCA AGAACACCCTGTATCTGCAGATGAACAGCCTGAGAGCCGAGGATACTGCTGTGTACTATTGCGCCAGGAATCTG GGCCCAAGCTTCTACTTTGACTATTGGGGGCAGGGAACACTGGTCACTGTGTCAAGCGCAGCCGAACCCAAATC CTCTGATAAGACTCACACCTGCCCACCTTGTCCAGCTCCAGAGCTGCTGGGAGGACCTAGCGTGTTCCTGTTTC CACCCAAGCCAAAAGACACTCTGATGATTTCTAGAACCCCTGAAGTGACATGTGTGGTCGTGGACGTCAGTCAC GAGGACCCCGAAGTCAAATTCAACTGGTACGTGGATGGCGTCGAGGTGCATAATGCCAAGACCAAACCCCGAGA GGAACAGTACAACTCAACCTATCGGGTCGTGAGCGTCCTGACAGTGCTGCATCAGGACTGGCTGAACGGCAAGG AGTATAAGTGCAAAGTGAGCAACAAGGCTCTGCCTGCACCAATCGAGAAGACCATTTCCAAGGCTAAAGGGCAG CCCCGCGAACCTCAGGTCTACGTGTATCCTCCAAGCCGAGATGAGCTGACAAAAAACCAGGTCTCCCTGACTTG TCTGGTGAAGGGATTTTACCCAAGTGACATCGCAGTGGAGTGGGAATCAAATGGCCAGCCCGAAAACAATTATA AGACCACACCCCCTGTGCTGGACTCTGATGGGAGTTTCGCACTGGTCTCCAAACTGACCGTGGACAAGTCTCGG TGGCAGCAGGGAAACGTCTTTAGCTGTTCCGTGATGCACGAGGCCCTGCACAATCATTACACACAGAAATCTCT GAGTCTGTCACCTGGCAAG
259	3317	VL	DIQMTQSPSSLSASVGDRVTITCKASQDVSIGVAWYQQKPGKAPKLLIYSASYRYTGVPSRFSGSGSGTDFTLT ISSLQPEDFATYYCQQYYIYPYTFGQGTKVEIK
260	3317	VL	GACATTCAGATGACCCAGAGCCCTAGCTCCCTGAGTGCCTCAGTCGGGGACAGGGTGACTATCACCTGCAAGGC TTCACAGGATGTCAGCATTGGCGTGGCATGGTACCAGCAGAAGCCAGGGAAAGCACCCAAGCTGCTGATCTATA GCGCCTCCTACAGGTATACAGGCGTGCCATCCCGCTTCTCTGGCAGTGGGTCAGGAACTGACTTTACACTGACT ATTTCTAGTCTGCAGCCCGAAGATTTCGCCACATACTATTGCCAGCAGTACTATATCTACCCTTATACTTTTGG CCAGGGGACCAAAGTGGAGATTAAG
261	3317	L1	QDVSIG
262	3317	L1	CAGGATGTCAGCATTGGC

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263	3317	L3	QQYYIYPYT
264	3317	L3	CAGCAGTACTATATCTACCCTTATACT
265	3317	L2	SAS
266	3317	L2	AGCGCCTCC
267	3317	VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFTDYTMDWVRQAPGKGLEWVADVNPNSGCSIYNQRFKGRFTLSVDR SKNTLYLQMNSLRAEDTAVYYCARNLGPSFYFDYWGQGTLVTVSS
268	3317	VH	GAGGTCCAGCTGGTGGAATCTGGAGGAGGACTGGTGCAGCCAGGAGGGTCCCTGAGGCTGTCTTGTGCCGCTAG TGGCTTCACCTTTACAGACTACACAATGGATTGGGTGCGCCAGGCACCAGGAAAGGGACTGGAATGGGTCGCTG ATGTGAACCCTAATAGCGGAGGCTCCATCTACAACCAGCGGTTCAAAGGACGGTTCACCCTGTCAGTGGACCGG AGCAAGAACACCCTGTATCTGCAGATGAACAGCCTGAGAGCCGAGGATACTGCTGTGTACTATTGCGCCAGGAA TCTGGGCCCAAGCTTCTACTTTGACTATTGGGGGCAGGGAACACTGGTCACTGTGTCAAGC
269	3317	H1	GFTFTDYT
270	3317	H1	GGCTTCACCTTTACAGACTACACA
271	3317	H3	ARNLGPSFYFDY
272	3317	H3	GCCAGGAATCTGGGCCCAAGCTTCTACTTTGACTAT
273	3317	H2	VNPNSGGS
274	3317	H2	GTGAACCCTAATAGCGGAGGCTCC
275	3317	CH2	APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK
276	3317	CH2	GCTCCAGAGCTGCTGGGAGGACCTAGCGTGTTCCTGTTTCCACCCAAGCCAAAAGACACTCTGATGATTTCTAG AACCCCTGAAGTGACATGTGTGGTCGTGGACGTCAGTCACGAGGACCCCGAAGTCAAATTCAACTGGTACGTGG ATGGCGTCGAGGTGCATAATGCCAAGACCAAACCCCGAGAGGAACAGTACAACTCAACCTATCGGGTCGTGAGC GTCCTGACAGTGCTGCATCAGGACTGGCTGAACGGCAAGGAGTATAAGTGCAAAGTGAGCAACAAGGCTCTGCC TGCACCAATCGAGAAGACCATTTCCAAGGCTAAA
277	3317	CH3	GQPREPQVYVYPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFALVSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
278	3317	CH3	GGGCAGCCCCGCGAACCTCAGGTCTACGTGTATCCTCCAAGCCGAGATGAGCTGACAAAAAACCAGGTCTCCCT GACTTGTCTGGTGAAGGGATTTTACCCAAGTGACATCGCAGTGGAGTGGGAATCAAATGGCCAGCCCGAAAACA ATTATAAGACCACACCCCCTGTGCTGGACTCTGATGGGAGTTTCGCACTGGTCTCCAAACTGACCGTGGACAAG TCTCGGTGGCAGCAGGGAAACGTCTTTAGCTGTTCCGTGATGCACGAGGCCCTGCACAATCATTACACACAGAA ATCTCTGAGTCTGTCACCTGGC
279	1015	Full	EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTISADT SKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKS CDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYVLPPSRDELTKNQVSLLC LVKGFYPSDIAVEWESNGQPENNYLTWPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL SLSPGK
280	1015	Full	GAGGTGCAGCTGGTGGAAAGCGGAGGAGGACTGGTGCAGCCAGGAGGATCTCTGCGACTGAGTTGCGCCGCTTC AGGATTCAACATCAAGGACACCTACATTCACTGGGTGCGACAGGCTCCAGGAAAAGGACTGGAGTGGGTGGCTC GAATCTATCCCACTAATGGATACACCCGGTATGCCGACTCCGTGAAGGGGAGGTTTACTATTAGCGCCGATACA TCCAAAAACACTGCTTACCTGCAGATGAACAGCCTGCGAGCCGAAGATACCGCTGTGTACTATTGCAGTCGATG GGGAGGAGACGGATTCTACGCTATGGATTATTGGGGACAGGGGACCCTGGTGACAGTGAGCTCCGCCTCTACCA AGGGCCCCAGTGTGTTTCCCCTGGCTCCTTCTAGTAAATCCACCTCTGGAGGGACAGCCGCTCTGGGATGTCTG GTGAAGGACTATTTCCCCGAGCCTGTGACCGTGAGTTGGAACTCAGGCGCCCTGACAAGCGGAGTGCACACTTT TCCTGCTGTGCTGCAGTCAAGCGGGCTGTACTCCCTGTCCTCTGTGGTGACAGTGCCAAGTTCAAGCCTGGGCA CACAGACTTATATCTGCAACGTGAATCATAAGCCCTCAAATACAAAAGTGGACAAGAAAGTGGAGCCCAAGAGC TGTGATAAGACCCACACCTGCCCTCCCTGTCCAGCTCCAGAACTGCTGGGAGGACCTAGCGTGTTCCTGTTTCC CCCTAAGCCAAAAGACACTCTGATGATTTCCAGGACTCCCGAGGTGACCTGCGTGGTGGTGGACGTGTCTCACG AGGACCCCGAAGTGAAGTTCAACTGGTACGTGGATGGCGTGGAAGTGCATAATGCTAAGACAAAACCAAGAGAG GAACAGTACAACTCCACTTATCGCGTCGTGAGCGTGCTGACCGTGCTGCACCAGGACTGGCTGAACGGGAAGGA GTATAAGTGCAAAGTCAGTAATAAGGCCCTGCCTGCTCCAATCGAAAAAACCATCTCTAAGGCCAAAGGCCAGC CAAGGGAGCCCCAGGTGTACGTGCTGCCACCCAGCAGAGACGAACTGACCAAGAACCAGGTGTCCCTGCTGTGT CTGGTGAAAGGCTTCTATCCTAGTGATATTGCTGTGGAGTGGGAATCAAATGGACAGCCAGAGAACAATTACCT GACCTGGCCTCCAGTGCTGGACAGCGATGGCAGCTTCTTCCTGTATTCCAAGCTGACAGTGGATAAATCTCGAT GGCAGCAGGGGAACGTGTTTAGTTGTTCAGTGATGCATGAAGCCCTGCACAATCATTACACTCAGAAGAGCCTG TCCCTGTCTCCCGGCAAA
281	1015	VH	EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTISADT SKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSS

SEQUENCE TABLE-continued

282	1015	VH	GAGGTGCAGCTGGTGGAAAGCGGAGGAGGACTGGTGCAGCCAGGAGGATCTCTGCGACTGAGTTGCGCCGCTTC AGGATTCAACATCAAGGACACCTACATTCACTGGGTGCGACAGGCTCCAGGAAAAGGACTGGAGTGGGTGGCTC GAATCTATCCCACTAATGGATACACCCGGTATGCCGACTCCGTGAAGGGGAGGTTTACTATTAGCGCCGATACA TCCAAAAACACTGCTTACCTGCAGATGAACAGCCTGCGAGCCGAAGATACCGCTGTGTACTATTGCAGTCGATG GGGAGGAGACGGATTCTACGCTATGGATTATTGGGGACAGGGGACCCTGGTGACAGTGAGCTCC
283	1015	H1	GFNIKDTY
284	1015	H1	GGATTCAACATCAAGGACACCTAC
285	1015	H3	SRWGGDGFYAMDY
286	1015	H3	AGTCGATGGGGAGGAGACGGATTCTACGCTATGGATTAT
287	1015	H2	IYPTNGYT
288	1015	H2	ATCTATCCCACTAATGGATACACC
289	1015	CH1	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHKPSNTKVDKKV
290	1015	CH1	GCCTCTACCAAGGGCCCCAGTGTGTTTCCCCTGGCTCCTTCTAGTAAATCCACCTCTGGAGGGACAGCCGCTCT GGGATGTCTGGTGAAGGACTATTTCCCCGAGCCTGTGACCGTGAGTTGGAACTCAGGCGCCCTGACAAGCGGAG TGCACACTTTTCCTGCTGTGCTGCAGTCAAGCGGGCTGTACTCCCTGTCCTCTGTGGTGACAGTGCCAAGTTCA AGCCTGGGCACACAGACTTATATCTGCAACGTGAATCATAAGCCCTCAAATACAAAAGTGGACAAGAAAGTG
291	1015	CH2	APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK
292	1015	CH2	GCTCCAGAACTGCTGGGAGGACCTAGCGTGTTCCTGTTTCCCCCTAAGCCAAAAGACACTCTGATGATTTCCAG GACTCCCGAGGTGACCTGCGTGGTGGTGGACGTGTCTCACGAGGACCCCGAAGTGAAGTTCAACTGGTACGTGG ATGGCGTGGAAGTGCATAATGCTAAGACAAAACCAAGAGAGGAACAGTACAACTCCACTTATCGCGTCGTGAGC GTGCTGACCGTGCTGCACCAGGACTGGCTGAACGGGAAGGAGTATAAGTGCAAAGTCAGTAATAAGGCCCTGCC TGCTCCAATCGAAAAAACCATCTCTAAGGCCAAA
293	1015	CH3	GQPREPQVYVLPPSRDELTKNQVSLLCLVKGFYPSDIAVEWESNGQPENNYLTWPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
294	1015	CH3	GGCCAGCCAAGGGAGCCCCAGGTGTACGTGCTGCCACCCAGCAGAGACGAACTGACCAAGAACCAGGTGTCCCT GCTGTGTCTGGTGAAAGGCTTCTATCCTAGTGATATTGCTGTGGAGTGGGAATCAAATGGACAGCCAGAGAACA ATTACCTGACCTGGCCTCCAGTGCTGGACAGCGATGGCAGCTTCTTCCTGTATTCCAAGCTGACAGTGGATAAA TCTCGATGGCAGCAGGGGAACGTGTTTAGTTGTTCAGTGATGCATGAAGCCCTGCACAATCATTACACTCAGAA GAGCCTGTCCCTGTCTCCCGGC
295	5244	Full	DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLT ISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIKGGSGGGSGGGSGGGSGGGSGEVQLVESGGGLVQPGGSLRLS CAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYY CSRWGGDGFYAMDYWGQGTLVTVSSAAEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI SKAKGQPREPQVYVLPPSRDELTKNQVSLLCLVKGFYPSDIAVEWESNGQPENNYLTWPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
296	5244	Full	GACATTCAGATGACACAGAGCCCCAGCTCCCTGAGTGCTTCAGTCGGCGACAGGGTGACTATCACCTGCCGCGC ATCCCAGGATGTCAACACCGCTGTGGCATGGTACCAGCAGAAGCCTGGAAAAGCCCCAAAGCTGCTGATCTACA GCGCTTCCTTCCTGTATTCTGGCGTGCCAAGTCGGTTTTCTGGAAGTAGATCAGGCACTGACTTCACACTGACT ATCTCTAGTCTGCAGCCCGAAGATTTTGCCACCTACTATTGCCAGCAGCACTATACCACACCCCCTACATTCGG ACAGGGCACTAAAGTGGAGATTAAGGGCGGGTCAGGCGGAGGGAGCGGAGGAGGGGTCCGGAGGAGGGTCTGGAG GAGGGAGTGGAGAGGTCCAGCTGGTGGAATCTGGAGGAGGACTGGTGCAGCCTGGAGGCTCACTGCGACTGAGC TGTGCCGCTTCCGGCTTTAACATCAAAGACACATACATTCATTGGGTCAGGCAGGCACCAGGGAAGGGACTGGA ATGGGTGGCCCGCATCTATCCCACAAATGGGTACACTCGATATGCCGACAGCGTGAAAGGACGGTTTACCATTT CTGCTGATACCAGTAAGAACACAGCATACCTGCAGATGAACAGCCTGCGCGCAGAGGATACAGCCGTGTACTAT TGCAGTCGATGGGGGGGAGACGGCTTCTACGCCATGGATTATTGGGGCCAGGGGACTCTGGTCACCGTGTCAAG CGCAGCCGAACCTAAATCCTCTGACAAGACCCACACATGCCCACCCTGTCCTGCTCCAGAGCTGCTGGGAGGAC CATCCGTGTTCCTGTTTCCTCCAAAGCCTAAAGATACACTGATGATTAGCCGCACTCCCGAAGTCACCTGTGTG GTCGTGGACGTGTCCCACGAGGACCCCGAAGTCAAGTTCAACTGGTACGTGGACGGCGTCGAGGTGCATAATGC CAAGACTAAACCAAGAGAGGAACAGTACAATTCAACCTATAGGGTCGTGAGCGTCCTGACAGTGCTGCATCAGG ATTGGCTGAACGGCAAGGAGTATAAGTGCAAAGTGTCTAACAAGGCCCTGCCCGCTCCTATCGAGAAGACTATT AGCAAGGCAAAAGGGCAGCCACGGGAACCCCAGGTCTACGTGCTGCCCCCTAGCAGAGACGAGCTGACCAAAAA CCAGGTCTCCCTGCTGTGTCTGGTGAAGGGCTTTTATCCTAGTGATATCGCTGTGGAGTGGGAATCAAATGGGC AGCCAGAAAACAATTACCTGACATGGCCACCCGTGCTGGACAGCGATGGGTCCTTCTTTCTGTATTCCAAACTG ACTGTGGACAAGTCTAGATGGCAGCAGGGAAACGTCTTCAGCTGTTCCGTGATGCACGAGGCCCTGCACAATCA TTACACCCAGAAGTCTCTGAGTCTGTCACCCGGC
297	5244	VL	DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLT ISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIK

SEQUENCE TABLE-continued

298	5244	VL	GACATTCAGATGACACAGAGCCCCAGCTCCCTGAGTGCTTCAGTCGGCGACAGGGTGACTATCACCTGCCGCGC ATCCCAGGATGTCAACACCGCTGTGGCATGGTACCAGCAGAAGCCTGGAAAAGCCCCAAAGCTGCTGATCTACA GCGCTTCCTTCCTGTATTCTGGCGTGCCAAGTCGGTTTTCTGGAAGTAGATCAGGCACTGACTTCACACTGACT ATCTCTAGTCTGCAGCCCGAAGATTTTGCCACCTACTATTGCCAGCAGCACTATACCACACCCCCTACATTCGG ACAGGGCACTAAAGTGGAGATTAAG
299	5244	L1	QDVNTA
300	5244	L1	CAGGATGTCAACACCGCT
301	5244	L3	QQHYTTPPT
302	5244	L3	CAGCAGCACTATACCACACCCCCTACA
303	5244	L2	SAS
304	5244	L2	AGCGCTTCC
305	5244	VH	EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTISADT SKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSS
306	5244	VH	GAGGTCCAGCTGGTGGAATCTGGAGGAGGACTGGTGCAGCCTGGAGGCTCACTGCGACTGAGCTGTGCCGCTTC CGGCTTTAACATCAAAGACACATACATTCATTGGGTCAGGCAGGCACCAGGGAAGGGACTGGAATGGGTGGCCC GCATCTATCCCACAAATGGGTACACTCGATATGCCGACAGCGTGAAAGGACGGTTTACCATTTCTGCTGATACC AGTAAGAACACAGCATACCTGCAGATGAACAGCCTGCGCGCAGAGGATACAGCCGTGTACTATTGCAGTCGATG GGGGGGAGACGGCTTCTACGCCATGGATTATTGGGGCCAGGGGACTCTGGTCACCGTGTCAAGC
307	5244	H1	GFNIKDTY
308	5244	H1	GGCTTTAACATCAAAGACACATAC
309	5244	H3	SRWGGDGFYAMDY
310	5244	H3	AGTCGATGGGGGGGAGACGGCTTCTACGCCATGGATTAT
311	5244	H2	IYPTNGYT
312	5244	H2	ATCTATCCCACAAATGGGTACACT
313	5244	CH2	APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK
314	5244	CH2	GCTCCAGAGCTGCTGGGAGGACCATCCGTGTTCCTGTTTCCTCCAAAGCCTAAAGATACACTGATGATTAGCCG CACTCCCGAAGTCACCTGTGTGGTCGTGGACGTGTCCCACGAGGACCCCGAAGTCAAGTTCAACTGGTACGTGG ACGGCGTCGAGGTGCATAATGCCAAGACTAAACCAAGAGAGGAACAGTACAATTCAACCTATAGGGTCGTGAGC GTCCTGACAGTGCTGCATCAGGATTGGCTGAACGGCAAGGAGTATAAGTGCAAAGTGTCTAACAAGGCCCTGCC CGCTCCTATCGAGAAGACTATTAGCAAGGCAAAA
315	5244	CH3	GQPREPQVYVLPPSRDELTKNQVSLLCLVKGFYPSDIAVEWESNGQPENNYLTWPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
316	5244	CH3	GGGCAGCCACGGGAACCCCAGGTCTACGTGCTGCCCCCTAGCAGAGACGAGCTGACCAAAAACCAGGTCTCCCT GCTGTGTCTGGTGAAGGGCTTTTATCCTAGTGATATCGCTGTGGAGTGGGAATCAAATGGGCAGCCAGAAAACA ATTACCTGACATGGCCACCCGTGCTGGACAGCGATGGGTCCTTCTTTCTGTATTCCAAACTGACTGTGGACAAG TCTAGATGGCAGCAGGGAAACGTCTTCAGCTGTTCCGTGATGCACGAGGCCCTGCACAATCATTACACCCAGAA GTCTCTGAGTCTGTCACCCGGC
317	-2	Full	DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLT ISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQW KVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
318	-2	Full	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGC AAGTCAGGACGTTAACACCGCTGTAGCTTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATT CTGCATCCTTTTTGTACAGTGGGGTCCCATCAAGGTTCAGTGGCAGTCGATCTGGGACAGATTTCACTCTCACC ATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGCATTACACTACCCCACCCACTTTCGG CCAAGGGACCAAAGTGGAGATCAAACGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGC AGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGG AAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAAGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTA CAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCC ATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT
319	-2	VL	DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLT ISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIK

SEQUENCE TABLE-continued

320	-2	VL	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGC AAGTCAGGACGTTAACACCGCTGTAGCTTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATT CTGCATCCTTTTTGTACAGTGGGGTCCCATCAAGGTTCAGTGGCAGTCGATCTGGGACAGATTTCACTCTCACC ATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGCATTACACTACCCCACCCACTTTCGG CCAAGGGACCAAAGTGGAGATCAAA
321	-2	L1	QDVNTA
322	-2	L1	CAGGACGTTAACACCGCT
323	-2	L3	QQHYTTPPT
324	-2	L3	CAACAGCATTACACTACCCCACCCACT
325	-2	L2	SAS
326	-2	L2	TCTGCATCC
327	-2	CL	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTL SKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
328	-2	CL	CGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGT TGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGG GTAACTCCCAAGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTG AGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCAC AAAGAGCTTCAACAGGGGAGAGTGT
329	4372	Full	EPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYVLPPSRDELTKNQV SLLCLVKGFYPSDIAVEWESNGQPENNYLTWPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPG
330	4372	Full	GAACCTAAATCCAGCGACAAGACCCACACATGCCCCCCTTGTCCAGCTCCAGAACTGCTGGGAGGACCAAGCGT GTTCCTGTTTCCACCCAAGCCCAAAGATACACTGATGATCAGCCGAACTCCCGAGGTCACCTGCGTGGTCGTGG ACGTGTCCCACGAGGACCCCGAAGTCAAGTTCAACTGGTACGTGGACGGCGTCGAAGTGCATAATGCAAAGACT AAACCACGGGAGGAACAGTACAACTCTACATATAGAGTCGTGAGTGTCCTGACTGTGCTGCATCAGGATTGGCT GAACGGCAAAGAGTATAAGTGCAAAGTGTCTAATAAGGCCCTGCCTGCTCCAATCGAGAAAACTATTAGTAAGG CAAAAGGGCAGCCCAGGGAACCTCAGGTCTACGTGCTGCCTCCAAGTCGCGACGAGCTGACCAAGAACCAGGTC TCACTGCTGTGTCTGGTGAAAGGATTCTATCCTTCCGATATTGCCGTGGAGTGGGAATCTAATGGCCAGCCAGA GAACAATTACCTGACCTGGCCCCCTGTGCTGGACAGCGATGGGTCCTTCTTTCTGTATTCAAAGCTGACAGTGG ACAAAAGCAGATGGCAGCAGGGAAACGTCTTTAGCTGTTCCGTGATGCACGAAGCCCTGCACAATCATTACACC CAGAAGTCTCTGAGTCTGTCACCTGGC
331	4372	CH2	APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK
332	4372	CH2	GCTCCAGAACTGCTGGGAGGACCAAGCGTGTTCCTGTTTCCACCCAAGCCCAAAGATACACTGATGATCAGCCG AACTCCCGAGGTCACCTGCGTGGTCGTGGACGTGTCCCACGAGGACCCCGAAGTCAAGTTCAACTGGTACGTGG ACGGCGTCGAAGTGCATAATGCAAAGACTAAACCACGGGAGGAACAGTACAACTCTACATATAGAGTCGTGAGT GTCCTGACTGTGCTGCATCAGGATTGGCTGAACGGCAAAGAGTATAAGTGCAAAGTGTCTAATAAGGCCCTGCC TGCTCCAATCGAGAAAACTATTAGTAAGGCAAAA
333	4372	CH3	GQPREPQVYVLPPSRDELTKNQVSLLCLVKGFYPSDIAVEWESNGQPENNYLTWPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
334	4372	CH3	GGGCAGCCCAGGGAACCTCAGGTCTACGTGCTGCCTCCAAGTCGCGACGAGCTGACCAAGAACCAGGTCTCACT GCTGTGTCTGGTGAAAGGATTCTATCCTTCCGATATTGCCGTGGAGTGGGAATCTAATGGCCAGCCAGAGAACA ATTACCTGACCTGGCCCCCTGTGCTGGACAGCGATGGGTCCTTCTTTCTGTATTCAAAGCTGACAGTGGACAAA AGCAGATGGCAGCAGGGAAACGTCTTTAGCTGTTCCGTGATGCACGAAGCCCTGCACAATCATTACACCCAGAA GTCTCTGAGTCTGTCACCTGGC

SEQ ID NO:	Pertuzumab WT CDR	sequences
335	CDR-H2	VNPNSGGS
336	CDR-H3	ARNLGPSFYFDY
337	CDR-H1	GFTFTDYT
338	CDR-L2	SAS
339	CDR-L3	QQYYIYPYT
340	CDR-L1	QDVSIG

SEQUENCE TABLE-continued

SEQ ID NO:	Trastuzumab WT CDR	sequences
341	CDR-H2	IYPTNGYT
342	CDR-H3	SRWGGDGFYAMDY
343	CDR-H1	GFNIKDTY
344	CDR-L2	SAS
345	CDR-L3	QQHYTTPPT
346	CDR-L1	QDVNTA

Pertuzumab variant CDR-L3: QQYYIYPAT
Clone 3382, variant 10000 (SEQ ID NO: 347)

Pertuzumab variant CDR-H1: GFTFADYT
Clone 6586, variant 10000 (SEQ ID NO: 348)

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 350

<210> SEQ ID NO 1
<211> LENGTH: 450
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 1

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Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr
            20                  25                  30

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
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        195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
    210                 215                 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225                 230                 235                 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                245                 250                 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            260                 265                 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        275                 280                 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
    290                 295                 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305                 310                 315                 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                325                 330                 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            340                 345                 350

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
        355                 360                 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385                 390                 395                 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                405                 410                 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            420                 425                 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        435                 440                 445

Gly Lys
    450


<210> SEQ ID NO 2
<211> LENGTH: 1350
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide

<400> SEQUENCE: 2

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agttgcgccg cttcaggatt caacatcaag gacacctaca ttcactgggt gcgacaggct    120

ccaggaaaag gactggagtg ggtggctcga atctatccca ctaatggata cacccggtat    180

gccgactccg tgaaggggag gtttactatt agcgccgata catccaaaaa cactgcttac    240

ctgcagatga acagcctgcg agccgaagat accgctgtgt actattgcag tcgatgggga    300

ggagacggat tctacgctat ggattattgg ggacagggga ccctggtgac agtgagctcc    360

gcctctacca agggccccag tgtgtttccc ctggctcctt ctagtaaatc cacctctgga    420

gggacagccg ctctgggatg tctggtgaag gactatttcc ccgagcctgt gaccgtgagt    480
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tggaactcag gcgccctgac aagcggagtg cacacttttc ctgctgtgct gcagtcaagc 540

gggctgtact ccctgtcctc tgtggtgaca gtgccaagtt caagcctggg cacacagact 600

tatatctgca acgtgaatca taagccctca aatacaaaag tggacaagaa agtggagccc 660

aagagctgtg ataagaccca cacctgccct ccctgtccag ctccagaact gctgggagga 720

cctagcgtgt tcctgtttcc ccctaagcca aaagacactc tgatgatttc caggactccc 780

gaggtgacct gcgtggtggt ggacgtgtct cacgaggacc ccgaagtgaa gttcaactgg 840

tacgtggatg gcgtggaagt gcataatgct aagacaaaac caagagagga acagtacaac 900

tccacttatc gcgtcgtgag cgtgctgacc gtgctgcacc aggactggct gaacgggaag 960

gagtataagt gcaaagtcag taataaggcc ctgcctgctc caatcgaaaa aaccatctct 1020

aaggccaaag gccagccaag ggagccccag gtgtacacac tgccacccag cagagacgaa 1080

ctgaccaaga accaggtgtc cctgacatgt ctggtgaaag gcttctatcc tagtgatatt 1140

gctgtggagt gggaatcaaa tggacagcca gagaacaatt acaagaccac acctccagtg 1200

ctggacagcg atggcagctt cttcctgtat tccaagctga cagtggataa atctcgatgg 1260

cagcagggga acgtgtttag ttgttcagtg atgcatgaag ccctgcacaa tcattacact 1320

cagaagagcc tgtccctgtc tcccggcaaa 1350

<210> SEQ ID NO 3
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 3

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr
20 25 30

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 4
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 4

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agttgcgccg cttcaggatt caacatcaag gacacctaca ttcactgggt gcgacaggct 120

ccaggaaaag gactggagtg ggtggctcga atctatccca ctaatggata cacccggtat 180

gccgactccg tgaaggggag gtttactatt agcgccgata catccaaaaa cactgcttac 240

ctgcagatga acagcctgcg agccgaagat accgctgtgt actattgcag tcgatgggga 300

ggagacggat tctacgctat ggattattgg ggacagggga ccctggtgac agtgagctcc 360

<210> SEQ ID NO 5
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 5

Gly Phe Asn Ile Lys Asp Thr Tyr
1 5

<210> SEQ ID NO 6
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 6

ggattcaaca tcaaggacac ctac 24

<210> SEQ ID NO 7
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 7

Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr
1 5 10

<210> SEQ ID NO 8
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 8

agtcgatggg gaggagacgg attctacgct atggattat 39

<210> SEQ ID NO 9
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

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<400> SEQUENCE: 9

Ile Tyr Pro Thr Asn Gly Tyr Thr
1 5

<210> SEQ ID NO 10
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 10

atctatccca ctaatggata cacc 24

<210> SEQ ID NO 11
<211> LENGTH: 98
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 11

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val

<210> SEQ ID NO 12
<211> LENGTH: 294
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 12

gcctctacca agggccccag tgtgtttccc ctggctcctt ctagtaaatc cacctctgga 60

gggacagccg ctctgggatg tctggtgaag gactatttcc ccgagcctgt gaccgtgagt 120

tggaactcag gcgccctgac aagcggagtg cacacttttc ctgctgtgct gcagtcaagc 180

gggctgtact ccctgtcctc tgtggtgaca gtgccaagtt caagcctggg cacacagact 240

tatatctgca acgtgaatca taagccctca aatacaaaag tggacaagaa agtg 294

<210> SEQ ID NO 13
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 13

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
50 55 60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
100 105 110

<210> SEQ ID NO 14
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 14

gctccagaac tgctgggagg acctagcgtg ttcctgtttc cccctaagcc aaaagacact 60

ctgatgattt ccaggactcc cgaggtgacc tgcgtggtgg tggacgtgtc tcacgaggac 120

cccgaagtga agttcaactg gtacgtggat ggcgtggaag tgcataatgc taagacaaaa 180

ccaagagagg aacagtacaa ctccacttat cgcgtcgtga gcgtgctgac cgtgctgcac 240

caggactggc tgaacgggaa ggagtataag tgcaaagtca gtaataaggc cctgcctgct 300

ccaatcgaaa aaaccatctc taaggccaaa 330

<210> SEQ ID NO 15
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 15

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
1 5 10 15

Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
20 25 30

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
35 40 45

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
50 55 60

Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
65 70 75 80

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr

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                85                  90                  95

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
            100                 105


<210> SEQ ID NO 16
<211> LENGTH: 318
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide

<400> SEQUENCE: 16

ggccagccaa gggagcccca ggtgtacaca ctgccaccca gcagagacga actgaccaag     60

aaccaggtgt ccctgacatg tctggtgaaa ggcttctatc ctagtgatat tgctgtggag    120

tgggaatcaa atggacagcc agagaacaat tacaagacca cacctccagt gctggacagc    180

gatggcagct tcttcctgta ttccaagctg acagtggata aatctcgatg gcagcagggg    240

aacgtgttta gttgttcagt gatgcatgaa gccctgcaca atcattacac tcagaagagc    300

ctgtccctgt ctcccggc                                                  318


<210> SEQ ID NO 17
<211> LENGTH: 448
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 17

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Asp Tyr
            20                  25                  30

Thr Met Asp Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asp Val Asn Pro Asn Ser Gly Gly Ser Ile Tyr Asn Gln Arg Phe
    50                  55                  60

Lys Gly Arg Phe Thr Leu Ser Val Asp Arg Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asn Leu Gly Pro Ser Phe Tyr Phe Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
        115                 120                 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
    130                 135                 140

Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145                 150                 155                 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
                165                 170                 175

Lys Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
            180                 185                 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
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        195                 200                 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
    210                 215                 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
            260                 265                 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
    290                 295                 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305                 310                 315                 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
                325                 330                 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val
            340                 345                 350

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Leu
        355                 360                 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
    370                 375                 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val Leu
385                 390                 395                 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
                405                 410                 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
            420                 425                 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440                 445


<210> SEQ ID NO 18
<211> LENGTH: 1344
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide

<400> SEQUENCE: 18

gaagtgcagc tggtcgaatc tggaggagga ctggtgcagc caggagggtc cctgcgcctg     60

tcttgcgccg ctagtggctt cacttttacc gactacacca tggattgggt gcgacaggca    120

cctggaaagg gcctggagtg ggtcgccgat gtgaacccaa atagcggagg ctccatctac    180

aaccagcggt tcaagggccg gttcaccctg tcagtggacc ggagcaaaaa caccctgtat    240

ctgcagatga atagcctgcg agccgaagat actgctgtgt actattgcgc ccggaatctg    300

gggccctcct tctactttga ctattggggg cagggaactc tggtcaccgt gagctccgcc    360

tccaccaagg gaccttctgt gttcccactg gctccctcta gtaaatccac atctgggggga    420

actgcagccc tgggctgtct ggtgaagggc tacttcccag agcccgtcac agtgtcttgg    480

aacagtggcg ctctgacttc tggggtccac acctttcctg cagtgctgaa gtcaagcggg    540
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ctgtacagcc tgtcctctgt ggtcaccgtg ccaagttcaa gcctgggaac acagacttat 600

atctgcaacg tgaatcacaa gccatccaat acaaaagtcg acaagaaagt ggaacccaag 660

tcttgtgata aaacccatac atgccccct tgtcctgcac cagagctgct gggaggacca 720

agcgtgttcc tgtttccacc caagcctaaa gatacactga tgattagtag gaccccagaa 780

gtcacatgcg tggtcgtgga cgtgagccac gaggaccccg aagtcaagtt taactggtac 840

gtggacggcg tcgaggtgca taatgccaag actaaaccca gggaggaaca gtacaacagt 900

acctatcgcg tcgtgtcagt cctgacagtg ctgcatcagg attggctgaa cgggaaagag 960

tataagtgca aagtgagcaa taaggctctg cccgcaccta tcgagaaaac aatttccaag 1020

gcaaaaggac agcctagaga accacaggtg tacgtgctgc ctccatcaag ggatgagctg 1080

acaaagaacc aggtcagcct gctgtgtctg gtgaaaggat tctatccctc tgacattgct 1140

gtggagtggg aaagtaatgg ccagcctgag aacaattacc tgacctggcc ccctgtgctg 1200

gactcagatg gcagcttctt tctgtatagc aagctgaccg tcgacaaatc ccggtggcag 1260

caggggaatg tgtttagttg ttcagtcatg cacgaggcac tgcacaacca ttacacccag 1320

aagtcactgt cactgtcacc aggg 1344

<210> SEQ ID NO 19
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 19

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Asp Tyr
20 25 30

Thr Met Asp Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asp Val Asn Pro Asn Ser Gly Gly Ser Ile Tyr Asn Gln Arg Phe
50 55 60

Lys Gly Arg Phe Thr Leu Ser Val Asp Arg Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asn Leu Gly Pro Ser Phe Tyr Phe Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> SEQ ID NO 20
<211> LENGTH: 357
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 20

gaagtgcagc tggtcgaatc tggaggagga ctggtgcagc caggagggtc cctgcgcctg 60

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tcttgcgccg ctagtggctt cacttttacc gactacacca tggattgggt gcgacaggca 120

cctggaaagg gcctggagtg ggtcgccgat gtgaacccaa atagcggagg ctccatctac 180

aaccagcggt tcaagggccg gttcaccctg tcagtggacc ggagcaaaaa caccctgtat 240

ctgcagatga atagcctgcg agccgaagat actgctgtgt actattgcgc ccggaatctg 300

gggccctcct tctactttga ctattggggg cagggaactc tggtcaccgt gagctcc 357

<210> SEQ ID NO 21
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 21

Gly Phe Thr Phe Thr Asp Tyr Thr
1 5

<210> SEQ ID NO 22
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 22

ggcttcactt ttaccgacta cacc 24

<210> SEQ ID NO 23
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 23

Ala Arg Asn Leu Gly Pro Ser Phe Tyr Phe Asp Tyr
1 5 10

<210> SEQ ID NO 24
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 24

gcccggaatc tggggccctc cttctacttt gactat 36

<210> SEQ ID NO 25
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 25

Val Asn Pro Asn Ser Gly Gly Ser

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1 5

<210> SEQ ID NO 26
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 26

gtgaacccaa atagcggagg ctcc 24

<210> SEQ ID NO 27
<211> LENGTH: 98
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 27

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Gly Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Lys Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val

<210> SEQ ID NO 28
<211> LENGTH: 294
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 28

gcctccacca agggaccttc tgtgttccca ctggctccct ctagtaaatc cacatctggg 60

ggaactgcag ccctgggctg tctggtgaag ggctacttcc cagagcccgt cacagtgtct 120

tggaacagtg gcgctctgac ttctggggtc cacacctttc ctgcagtgct gaagtcaagc 180

gggctgtaca gcctgtcctc tgtggtcacc gtgccaagtt caagcctggg aacacagact 240

tatatctgca acgtgaatca caagccatcc aatacaaaag tcgacaagaa agtg 294

<210> SEQ ID NO 29
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

-continued

<400> SEQUENCE: 29

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
50 55 60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
100 105 110

<210> SEQ ID NO 30
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 30

gcaccagagc tgctgggagg accaagcgtg ttcctgtttc cacccaagcc taaagataca 60

ctgatgatta gtaggacccc agaagtcaca tgcgtggtcg tggacgtgag ccacgaggac 120

cccgaagtca agtttaactg gtacgtggac ggcgtcgagg tgcataatgc caagactaaa 180

cccagggagg aacagtacaa cagtacctat cgcgtcgtgt cagtcctgac agtgctgcat 240

caggattggc tgaacgggaa agagtataag tgcaaagtga gcaataaggc tctgcccgca 300

cctatcgaga aaacaatttc caaggcaaaa 330

<210> SEQ ID NO 31
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 31

Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Leu Pro Pro Ser Arg Asp
1 5 10 15

Glu Leu Thr Lys Asn Gln Val Ser Leu Leu Cys Leu Val Lys Gly Phe
20 25 30

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
35 40 45

Asn Asn Tyr Leu Thr Trp Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
50 55 60

Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
65 70 75 80

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
85 90 95

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly

-continued

100 105

<210> SEQ ID NO 32
<211> LENGTH: 318
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 32

ggacagccta gagaaccaca ggtgtacgtg ctgcctccat caagggatga gctgacaaag 60

aaccaggtca gcctgctgtg tctggtgaaa ggattctatc cctctgacat tgctgtggag 120

tgggaaagta atggccagcc tgagaacaat tacctgacct ggccccctgt gctggactca 180

gatggcagct tctttctgta tagcaagctg accgtcgaca aatcccggtg gcagcagggg 240

aatgtgttta gttgttcagt catgcacgag gcactgcaca accattacac ccagaagtca 300

ctgtcactgt caccaggg 318

<210> SEQ ID NO 33
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 33

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Ile Gly
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Ile Tyr Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys

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210

<210> SEQ ID NO 34
<211> LENGTH: 642
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 34

gatattcaga tgacccagtc cccaagctcc ctgagtgcct cagtgggcga ccgagtcacc 60

atcacatgca aggcttccca ggatgtgtct attggagtcg catggtacca gcagaagcca 120

ggcaaagcac ccaagctgct gatctatagc gcctcctacc ggtataccgg cgtgccctct 180

agattctctg gcagtgggtc aggaacagac tttactctga ccatctctag tctgcagcct 240

gaggatttcg ctacctacta ttgccagcag tactatatct acccatatac ctttggccag 300

gggacaaaag tggagatcaa gaggactgtg gccgctccct ccgtcttcat ttttccccct 360

tctgacgaac agctgaaaag tggcacagcc agcgtggtct gtctgctgaa caatttctac 420

cctcgcgaag ccaaagtgca gtggaaggtc gataacgctc tgcagagcgg caacagccag 480

gagtctgtga ctgaacagga cagtaaagat tcaacctata gcctgtcaag cacactgact 540

ctgagcaagg cagactacga gaagcacaaa gtgtatgcct gcgaagtcac acatcagggg 600

ctgtcctctc ctgtgactaa gagctttaac agaggagagt gt 642

<210> SEQ ID NO 35
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 35

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Ile Gly
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Ile Tyr Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 36
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

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<400> SEQUENCE: 36

gatattcaga tgacccagtc cccaagctcc ctgagtgcct cagtgggcga ccgagtcacc 60

atcacatgca aggcttccca ggatgtgtct attggagtcg catggtacca gcagaagcca 120

ggcaaagcac ccaagctgct gatctatagc gcctcctacc ggtataccgg cgtgccctct 180

agattctctg gcagtgggtc aggaacagac tttactctga ccatctctag tctgcagcct 240

gaggatttcg ctacctacta ttgccagcag tactatatct acccatatac ctttggccag 300

gggacaaaag tggagatcaa g 321

<210> SEQ ID NO 37
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 37

Gln Asp Val Ser Ile Gly
1 5

<210> SEQ ID NO 38
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 38

caggatgtgt ctattgga 18

<210> SEQ ID NO 39
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 39

Gln Gln Tyr Tyr Ile Tyr Pro Tyr Thr
1 5

<210> SEQ ID NO 40
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 40

cagcagtact atatctaccc atatacc 27

<210> SEQ ID NO 41
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

-continued

<400> SEQUENCE: 41

Ser Ala Ser
1

<210> SEQ ID NO 42
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 42

agcgcctcc 9

<210> SEQ ID NO 43
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 43

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
1 5 10 15

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
20 25 30

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
35 40 45

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
50 55 60

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
65 70 75 80

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
85 90 95

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
100 105

<210> SEQ ID NO 44
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 44

aggactgtgg ccgctccctc cgtcttcatt tttccccctt ctgacgaaca gctgaaaagt 60

ggcacagcca gcgtggtctg tctgctgaac aatttctacc ctcgcgaagc caaagtgcag 120

tggaaggtcg ataacgctct gcagagcggc aacagccagg agtctgtgac tgaacaggac 180

agtaaagatt caacctatag cctgtcaagc acactgactc tgagcaaggc agactacgag 240

aagcacaaag tgtatgcctg cgaagtcaca catcaggggc tgtcctctcc tgtgactaag 300

agctttaaca gaggagagtg t 321

<210> SEQ ID NO 45

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<211> LENGTH: 222
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 45

Asp Tyr Lys Asp Asp Asp Asp Lys Asp Ile Gln Met Thr Gln Ser Pro
1 5 10 15

Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg
20 25 30

Ala Ser Gln Asp Val Asn Thr Ala Val Ala Trp Tyr Gln Gln Lys Pro
35 40 45

Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ser Ala Ser Phe Leu Tyr Ser
50 55 60

Gly Val Pro Ser Arg Phe Ser Gly Ser Arg Ser Gly Thr Asp Phe Thr
65 70 75 80

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
85 90 95

Gln Gln His Tyr Thr Thr Pro Pro Thr Phe Gly Gln Gly Thr Lys Val
100 105 110

Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro
115 120 125

Ser Asp Glu Arg Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu
130 135 140

Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn
145 150 155 160

Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser
165 170 175

Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala
180 185 190

Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly
195 200 205

Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215 220

<210> SEQ ID NO 46
<211> LENGTH: 666
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 46

gactacaaag acgacgatga caaagatatc cagatgaccc agtcccctag ctccctgtcc 60

gcttctgtgg gcgatagggt cactattacc tgccgcgcat ctcaggacgt gaacaccgca 120

gtcgcctggt accagcagaa gcctgggaaa gctccaaagc tgctgatcta cagtgcatca 180

ttcctgtatt caggagtgcc cagccggttt agcggcagca gatctggcac cgatttcaca 240

ctgactattt ctagtctgca gcctgaggac tttgccacat actattgcca gcagcactat 300

accacacccc ctactttcgg ccaggggacc aaagtggaga tcaagcgaac tgtggccgct 360

ccaagtgtct tcatttttcc acccagcgat gaaagactga agtccggcac agcttctgtg 420

-continued

gtctgtctgc tgaacaattt ttaccccaga gaggccaaag tgcagtggaa ggtcgacaac 480

gctctgcaga gtggcaacag ccaggagagc gtgacagaac aggattccaa agactctact 540

tatagtctgt caagcaccct gacactgagc aaggcagact acgaaaagca taaagtgtat 600

gcctgtgagg tcacacatca ggggctgtca tcaccagtca ccaaatcatt caatcggggg 660

gagtgc 666

<210> SEQ ID NO 47
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 47

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Asn Thr Ala
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Pro
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 48
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 48

gatatccaga tgacccagtc ccctagctcc ctgtccgctt ctgtgggcga tagggtcact 60

attacctgcc gcgcatctca ggacgtgaac accgcagtcg cctggtacca gcagaagcct 120

gggaaagctc caaagctgct gatctacagt gcatcattcc tgtattcagg agtgcccagc 180

cggtttagcg gcagcagatc tggcaccgat ttcacactga ctatttctag tctgcagcct 240

gaggactttg ccacatacta ttgccagcag cactatacca cacccctac tttcggccag 300

gggaccaaag tggagatcaa g 321

<210> SEQ ID NO 49
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 49

-continued

Gln Asp Val Asn Thr Ala
1 5

<210> SEQ ID NO 50
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 50

caggacgtga acaccgca 18

<210> SEQ ID NO 51
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 51

Gln Gln His Tyr Thr Thr Pro Pro Thr
1 5

<210> SEQ ID NO 52
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 52

cagcagcact ataccacacc ccctact 27

<210> SEQ ID NO 53
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 53

Ser Ala Ser
1

<210> SEQ ID NO 54
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 54

agtgcatca 9

<210> SEQ ID NO 55
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 55

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
1 5 10 15

Arg Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
20 25 30

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
35 40 45

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
50 55 60

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
65 70 75 80

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
85 90 95

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
100 105

<210> SEQ ID NO 56
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 56

cgaactgtgg ccgctccaag tgtcttcatt tttccaccca gcgatgaaag actgaagtcc 60

ggcacagctt ctgtggtctg tctgctgaac aatttttacc ccagagaggc caaagtgcag 120

tggaaggtcg acaacgctct gcagagtggc aacagccagg agagcgtgac agaacaggat 180

tccaaagact ctacttatag tctgtcaagc accctgacac tgagcaaggc agactacgaa 240

aagcataaag tgtatgcctg tgaggtcaca catcaggggc tgtcatcacc agtcaccaaa 300

tcattcaatc gggggagtg c 321

<210> SEQ ID NO 57
<211> LENGTH: 222
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 57

Asp Tyr Lys Asp Asp Asp Asp Lys Asp Ile Gln Met Thr Gln Ser Pro
1 5 10 15

Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg
20 25 30

Ala Ser Gln Asp Val Asn Thr Ala Val Ala Trp Tyr Gln Gln Lys Pro
35 40 45

Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ser Ala Ser Phe Leu Tyr Ser
50 55 60

Gly Val Pro Ser Arg Phe Ser Gly Ser Arg Ser Gly Thr Asp Phe Thr
65 70 75 80

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys

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               85                  90                  95

Gln Gln His Tyr Thr Thr Pro Pro Thr Phe Gly Gln Gly Thr Lys Val
            100                 105                 110

Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro
        115                 120                 125

Ser Asp Glu Arg Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu
    130                 135                 140

Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn
145                 150                 155                 160

Ala Leu Gln Ser Gly Asn Ser Lys Glu Ser Val Thr Glu Gln Asp Ser
                165                 170                 175

Lys Asp Ser Thr Tyr Ser Leu Ser Ser Arg Leu Thr Leu Ser Lys Ala
            180                 185                 190

Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly
        195                 200                 205

Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215                 220


<210> SEQ ID NO 58
<211> LENGTH: 666
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide

<400> SEQUENCE: 58

gactacaaag acgacgatga caaagatatc cagatgaccc agtcccctag ctccctgtcc     60

gcttctgtgg gcgatagggt cactattacc tgccgcgcat ctcaggacgt gaacaccgca    120

gtcgcctggt accagcagaa gcctgggaaa gctccaaagc tgctgatcta cagtgcatca    180

ttcctgtatt caggagtgcc cagccggttt agcggcagca gatctggcac cgatttcaca    240

ctgactattt ctagtctgca gcctgaggac tttgccacat actattgcca gcagcactat    300

accacacccc ctactttcgg ccaggggacc aaagtggaga tcaagcgaac tgtggccgct    360

ccaagtgtct tcatttttcc acccagcgat gaaagactga agtccggcac agcttctgtg    420

gtctgtctgc tgaacaattt ttaccccaga gaggccaaag tgcagtggaa ggtcgacaac    480

gctctgcaga gtggcaacag caaggagagc gtgacagaac aggattccaa agactctact    540

tatagtctgt caagcagact gacactgagc aaggcagact acgaaaagca taaagtgtat    600

gcctgtgagg tcacacatca ggggctgtca tcaccagtca ccaaatcatt caatcggggg    660

gagtgc                                                               666


<210> SEQ ID NO 59
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 59

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Asn Thr Ala
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            20                  25                  30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
        50                  55                  60

Ser Arg Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Pro
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 60
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide

<400> SEQUENCE: 60

gatatccaga tgacccagtc ccctagctcc ctgtccgctt ctgtgggcga tagggtcact     60

attacctgcc gcgcatctca ggacgtgaac accgcagtcg cctggtacca gcagaagcct    120

gggaaagctc caaagctgct gatctacagt gcatcattcc tgtattcagg agtgcccagc    180

cggtttagcg gcagcagatc tggcaccgat ttcacactga ctatttctag tctgcagcct    240

gaggactttg ccacatacta ttgccagcag cactatacca cacccctac tttcggccag    300

gggaccaaag tggagatcaa g                                              321


<210> SEQ ID NO 61
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      peptide

<400> SEQUENCE: 61

Gln Asp Val Asn Thr Ala
1               5


<210> SEQ ID NO 62
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      oligonucleotide

<400> SEQUENCE: 62

caggacgtga acaccgca                                                  18


<210> SEQ ID NO 63
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      peptide
```

-continued

<400> SEQUENCE: 63

Gln Gln His Tyr Thr Thr Pro Pro Thr
1 5

<210> SEQ ID NO 64
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 64

cagcagcact ataccacacc ccctact 27

<210> SEQ ID NO 65
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 65

Ser Ala Ser
1

<210> SEQ ID NO 66
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 66

agtgcatca 9

<210> SEQ ID NO 67
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 67

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
1 5 10 15

Arg Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
20 25 30

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
35 40 45

Ser Gly Asn Ser Lys Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
50 55 60

Thr Tyr Ser Leu Ser Ser Arg Leu Thr Leu Ser Lys Ala Asp Tyr Glu
65 70 75 80

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
85 90 95

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
100 105

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<210> SEQ ID NO 68
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 68

cgaactgtgg ccgctccaag tgtcttcatt tttccaccca gcgatgaaag actgaagtcc 60

ggcacagctt ctgtggtctg tctgctgaac aatttttacc ccagagaggc caaagtgcag 120

tggaaggtcg acaacgctct gcagagtggc aacagcaagg agagcgtgac agaacaggat 180

tccaaagact ctacttatag tctgtcaagc agactgacac tgagcaaggc agactacgaa 240

aagcataaag tgtatgcctg tgaggtcaca catcaggggc tgtcatcacc agtcaccaaa 300

tcattcaatc gggggggagtg c 321

<210> SEQ ID NO 69
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 69

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Ile Gly
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Ile Tyr Pro Ala
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

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<210> SEQ ID NO 70
<211> LENGTH: 642
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 70

gatattcaga tgacccagtc cccaagctcc ctgagtgcct cagtgggcga ccgagtcacc 60

atcacatgca aggcttccca ggatgtgtct attggagtcg catggtacca gcagaagcca 120

ggcaaagcac ccaagctgct gatctatagc gcctcctacc ggtataccgg cgtgccctct 180

agattctctg gcagtgggtc aggaacagac tttactctga ccatctctag tctgcagcct 240

gaggatttcg ctacctacta ttgccagcag tactatatct acccagccac ctttggccag 300

gggacaaaag tggagatcaa gaggactgtg gccgctccct ccgtcttcat ttttccccct 360

tctgacgaac agctgaaaag tggcacagcc agcgtggtct gtctgctgaa caatttctac 420

cctcgcgaag ccaaagtgca gtggaaggtc gataacgctc tgcagagcgg caacagccag 480

gagtctgtga ctgaacagga cagtaaagat tcaacctata gcctgtcaag cacactgact 540

ctgagcaagg cagactacga gaagcacaaa gtgtatgcct gcgaagtcac acatcagggg 600

ctgtcctctc ctgtgactaa gagctttaac agaggagagt gt 642

<210> SEQ ID NO 71
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 71

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Ile Gly
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Ile Tyr Pro Ala
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 72
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 72

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gatattcaga tgacccagtc cccaagctcc ctgagtgcct cagtgggcga ccgagtcacc 60

atcacatgca aggcttccca ggatgtgtct attggagtcg catggtacca gcagaagcca 120

ggcaaagcac ccaagctgct gatctatagc gcctcctacc ggtataccgg cgtgccctct 180

agattctctg gcagtgggtc aggaacagac tttactctga ccatctctag tctgcagcct 240

gaggatttcg ctacctacta ttgccagcag tactatatct acccagccac ctttggccag 300

gggacaaaag tggagatcaa g 321

<210> SEQ ID NO 73
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 73

Gln Asp Val Ser Ile Gly
1 5

<210> SEQ ID NO 74
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 74

caggatgtgt ctattgga 18

<210> SEQ ID NO 75
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 75

Gln Gln Tyr Tyr Ile Tyr Pro Ala Thr
1 5

<210> SEQ ID NO 76
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 76

cagcagtact atatctaccc agccacc 27

<210> SEQ ID NO 77
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

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<400> SEQUENCE: 77

Ser Ala Ser
1

<210> SEQ ID NO 78
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 78

agcgcctcc 9

<210> SEQ ID NO 79
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 79

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
1 5 10 15

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
20 25 30

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
35 40 45

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
50 55 60

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
65 70 75 80

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
85 90 95

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
100 105

<210> SEQ ID NO 80
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 80

aggactgtgg ccgctccctc cgtcttcatt tttccccctt ctgacgaaca gctgaaaagt 60

ggcacagcca gcgtggtctg tctgctgaac aatttctacc ctcgcgaagc caaagtgcag 120

tggaaggtcg ataacgctct gcagagcggc aacagccagg agtctgtgac tgaacaggac 180

agtaaagatt caacctatag cctgtcaagc acactgactc tgagcaaggc agactacgag 240

aagcacaaag tgtatgcctg cgaagtcaca catcaggggc tgtcctctcc tgtgactaag 300

agctttaaca gaggagagtg t 321

<210> SEQ ID NO 81
<211> LENGTH: 449

-continued

<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 81

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr
20 25 30

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

Leu Gly Cys Glu Val Thr Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
290 295 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Val Tyr Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
355 360 365

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Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385                 390                 395                 400

Leu Asp Ser Asp Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp
                405                 410                 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            420                 425                 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        435                 440                 445

Gly
```

<210> SEQ ID NO 82
<211> LENGTH: 1347
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 82

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gaggtgcagc tggtcgaaag cggaggagga ctggtgcagc caggagggtc actgcgactg     60

agctgcgcag cttccggctt caacatcaag gacacctaca ttcactgggt ccgccaggct    120

cctggaaaag gcctggagtg ggtggcacga atctatccaa ctaatggata cacccggtat    180

gccgactccg tgaagggccg gttcaccatt tctgcagata caagtaaaaa cactgcctac    240

ctgcagatga acagcctgcg agccgaagat acagccgtgt actattgcag ccgatgggga    300

ggcgacggct tctacgctat ggattattgg gggcagggaa ccctggtcac agtgagctcc    360

gcatcaacaa aggggcctag cgtgtttcca ctggcccccc ctagtaaatc cacctctggg    420

ggaacagcag ccctgggatg tgaggtgacc gactacttcc cagagcccgt cactgtgagc    480

tggaactccg gcgccctgac atctggggtc catacttttc ctgctgtgct gcagtcaagc    540

ggcctgtaca gcctgtcctc tgtggtcact gtgccaagtt caagcctggg gactcagacc    600

tatatctgca acgtgaatca caagccatcc aataccaaag tcgacaagaa agtggaaccc    660

aagtcttgtg ataaaacaca tacttgcccc ccttgtcctg caccagagct gctgggagga    720

ccaagcgtgt tcctgtttcc acccaagcct aaagacaccc tgatgattag taggactcca    780

gaagtcacct gcgtggtcgt ggacgtgagc cacgaggacc ccgaagtcaa gttcaactgg    840

tacgtggatg gcgtcgaggt gcataatgcc aagacaaaac ccagggagga acagtacaac    900

tccacttatc gcgtcgtgtc tgtcctgacc gtgctgcacc aggactggct gaacggcaag    960

gagtataagt gcaaagtgag caataaggct ctgcccgcac ctatcgagaa aacaatttcc   1020

aaggctaaag ggcagcctag agaaccacag gtgtacgtgt accctccatc tagggacgag   1080

ctgaccaaga accaggtcag tctgacatgt ctggtgaaag ggttctatcc cagcgatatc   1140

gcagtggagt gggaatccaa tggacagcct gagaacaatt acaagaccac acccccctgtg   1200

ctggactctg atggaagttt cgccctggtg agtaagctga ccgtcgataa atcacggtgg   1260

cagcagggca acgtgttcag ctgttcagtg atgcacgaag cactgcacaa ccactacacc   1320

cagaaaagcc tgtccctgtc ccccggc                                       1347
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<210> SEQ ID NO 83
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 83

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr
20 25 30

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 84
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 84

gaggtgcagc tggtcgaaag cggaggagga ctggtgcagc caggagggtc actgcgactg 60

agctgcgcag cttccggctt caacatcaag gacacctaca ttcactgggt ccgccaggct 120

cctggaaaag gcctggagtg ggtggcacga atctatccaa ctaatggata cacccggtat 180

gccgactccg tgaagggccg gttcaccatt tctgcagata caagtaaaaa cactgcctac 240

ctgcagatga acagcctgcg agccgaagat acagccgtgt actattgcag ccgatgggga 300

ggcgacggct tctacgctat ggattattgg gggcagggaa ccctggtcac agtgagctcc 360

<210> SEQ ID NO 85
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 85

Gly Phe Asn Ile Lys Asp Thr Tyr
1 5

<210> SEQ ID NO 86
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 86

ggcttcaaca tcaaggacac ctac 24

<210> SEQ ID NO 87
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 87

Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr
1 5 10

<210> SEQ ID NO 88
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 88

agccgatggg gaggcgacgg cttctacgct atggattat 39

<210> SEQ ID NO 89
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 89

Ile Tyr Pro Thr Asn Gly Tyr Thr
1 5

<210> SEQ ID NO 90
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 90

atctatccaa ctaatggata cacc 24

<210> SEQ ID NO 91
<211> LENGTH: 98
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 91

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

-continued

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Glu Val Thr Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val

<210> SEQ ID NO 92
<211> LENGTH: 294
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 92

gcatcaacaa aggggcctag cgtgtttcca ctggcccccct ctagtaaatc cacctctggg 60

ggaacagcag ccctgggatg tgaggtgacc gactacttcc cagagcccgt cactgtgagc 120

tggaactccg gcgccctgac atctggggtc catacttttc ctgctgtgct gcagtcaagc 180

ggcctgtaca gcctgtcctc tgtggtcact gtgccaagtt caagcctggg gactcagacc 240

tatatctgca acgtgaatca caagccatcc aataccaaag tcgacaagaa agtg 294

<210> SEQ ID NO 93
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 93

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
50 55 60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
100 105 110

<210> SEQ ID NO 94
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

-continued

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 94

gcaccagagc tgctgggagg accaagcgtg ttcctgtttc cacccaagcc taaagacacc 60

ctgatgatta gtaggactcc agaagtcacc tgcgtggtcg tggacgtgag ccacgaggac 120

cccgaagtca agttcaactg gtacgtggat ggcgtcgagg tgcataatgc caagacaaaa 180

cccagggagg aacagtacaa ctccacttat cgcgtcgtgt ctgtcctgac cgtgctgcac 240

caggactggc tgaacggcaa ggagtataag tgcaaagtga gcaataaggc tctgcccgca 300

cctatcgaga aaacaatttc caaggctaaa 330

<210> SEQ ID NO 95
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 95

Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr Pro Pro Ser Arg Asp
1 5 10 15

Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
20 25 30

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
35 40 45

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
50 55 60

Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
65 70 75 80

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
85 90 95

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
100 105

<210> SEQ ID NO 96
<211> LENGTH: 318
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 96

gggcagccta gagaaccaca ggtgtacgtg taccctccat ctagggacga gctgaccaag 60

aaccaggtca gtctgacatg tctggtgaaa gggttctatc ccagcgatat cgcagtggag 120

tgggaatcca atggacagcc tgagaacaat tacaagacca cacccctgt gctggactct 180

gatggaagtt tcgccctggt gagtaagctg accgtcgata aatcacggtg gcagcagggc 240

aacgtgttca gctgttcagt gatgcacgaa gcactgcaca accactacac ccagaaaagc 300

ctgtccctgt cccccggc 318

<210> SEQ ID NO 97
<211> LENGTH: 448
<212> TYPE: PRT

-continued

<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 97

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ala Asp Tyr
            20                  25                  30

Thr Met Asp Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Gly Asp Val Asn Pro Asn Ser Gly Gly Ser Ile Tyr Asn Gln Arg Phe
    50                  55                  60

Lys Gly Arg Phe Thr Phe Ser Val Asp Arg Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asn Leu Gly Pro Ser Phe Tyr Phe Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
        115                 120                 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
    130                 135                 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145                 150                 155                 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
                165                 170                 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
            180                 185                 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
        195                 200                 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
    210                 215                 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
            260                 265                 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
    290                 295                 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305                 310                 315                 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
                325                 330                 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val
            340                 345                 350

Tyr Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
        355                 360                 365
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Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
    370                 375                 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385                 390                 395                 400

Asp Ser Asp Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp Lys
                405                 410                 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
            420                 425                 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440                 445
```

<210> SEQ ID NO 98
<211> LENGTH: 1344
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 98

```
gaggtgcagc tggtggaatc aggagggggc ctggtgcagc ccggagggtc tctgcgactg     60

tcatgtgccg cttctgggtt cactttcgca gactacacaa tggattgggt gcgacaggcc    120

cccggaaagg gactggagtg ggtgggcgat gtcaacccta attctggcgg gagtatctac    180

aaccagcggt tcaaggggag attcactttt tcagtggaca gaagcaaaaa caccctgtat    240

ctgcagatga acagcctgag ggccgaagat accgctgtct actattgcgc tcgcaatctg    300

ggccccagtt tctactttga ctattggggg cagggaaccc tggtgacagt cagctccgct    360

agcactaagg ggccttccgt gtttccactg gctccctcta gtaaatccac ctctggaggc    420

acagctgcac tgggatgtct ggtgaaggat tacttccctg aaccagtcac agtgagttgg    480

aactcagggg ctctgacaag tggagtccat acttttcccg cagtgctgca gtcaagcgga    540

ctgtactccc tgtcctctgt ggtcaccgtg cctagttcaa gcctgggcac ccagacatat    600

atctgcaacg tgaatcacaa gccatcaaat acaaaagtcg acaagaaagt ggagcccaag    660

agctgtgata aaactcatac ctgcccacct tgtccggcgc cagaactgct gggaggacca    720

agcgtgttcc tgtttccacc caagcctaaa gacaccctga tgatttcccg gactcctgag    780

gtcacctgcg tggtcgtgga cgtgtctcac gaggaccccg aagtcaagtt caactggtac    840

gtggatggcg tcgaagtgca taatgccaag accaaacccc gggaggaaca gtacaactct    900

acctatagag tcgtgagtgt cctgacagtg ctgcaccagg actggctgaa tgggaaggag    960

tataagtgta aagtgagcaa caaagccctg cccgccccaa tcgaaaaaac aatctctaaa   1020

gcaaaaggac agcctcgcga accacaggtc tacgtctacc ccccatcaag agatgaactg   1080

acaaaaaatc aggtctctct gacatgcctg gtcaaaggat tctacccttc cgacatcgcc   1140

gtggagtggg aaagtaacgg ccagcccgag aacaattaca agaccacacc ccctgtcctg   1200

gactctgatg ggagtttcgc tctggtgtca aagctgaccg tcgataaaag ccggtggcag   1260

cagggcaatg tgtttagctg ctccgtcatg cacgaagccc tgcacaatca ctacacacag   1320

aagtccctga gcctgagccc tggc                                          1344
```

<210> SEQ ID NO 99
<211> LENGTH: 119
<212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 99

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ala Asp Tyr
20 25 30

Thr Met Asp Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Asp Val Asn Pro Asn Ser Gly Gly Ser Ile Tyr Asn Gln Arg Phe
50 55 60

Lys Gly Arg Phe Thr Phe Ser Val Asp Arg Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asn Leu Gly Pro Ser Phe Tyr Phe Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> SEQ ID NO 100
<211> LENGTH: 357
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 100

gaggtgcagc tggtggaatc aggagggggc ctggtgcagc ccggagggtc tctgcgactg 60

tcatgtgccg cttctgggtt cactttcgca gactacacaa tggattgggt gcgacaggcc 120

cccggaaagg gactggagtg ggtgggcgat gtcaacccta attctggcgg gagtatctac 180

aaccagcggt tcaaggggag attcactttt tcagtggaca gaagcaaaaa caccctgtat 240

ctgcagatga acagcctgag ggccgaagat accgctgtct actattgcgc tcgcaatctg 300

ggccccagtt tctactttga ctattgggggg cagggaaccc tggtgacagt cagctcc 357

<210> SEQ ID NO 101
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 101

Gly Phe Thr Phe Ala Asp Tyr Thr
1 5

<210> SEQ ID NO 102
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

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<400> SEQUENCE: 102

gggttcactt tcgcagacta caca 24

<210> SEQ ID NO 103
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 103

Ala Arg Asn Leu Gly Pro Ser Phe Tyr Phe Asp Tyr
1 5 10

<210> SEQ ID NO 104
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 104

gctcgcaatc tgggccccag tttctacttt gactat 36

<210> SEQ ID NO 105
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 105

Val Asn Pro Asn Ser Gly Gly Ser
1 5

<210> SEQ ID NO 106
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 106

gtcaacccta attctggcgg gagt 24

<210> SEQ ID NO 107
<211> LENGTH: 98
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 107

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

-continued

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val

<210> SEQ ID NO 108
<211> LENGTH: 294
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 108

gctagcacta aggggccttc cgtgtttcca ctggctccct ctagtaaatc cacctctgga 60

ggcacagctg cactgggatg tctggtgaag gattacttcc ctgaaccagt cacagtgagt 120

tggaactcag gggctctgac aagtggagtc catacttttc ccgcagtgct gcagtcaagc 180

ggactgtact ccctgtcctc tgtggtcacc gtgcctagtt caagcctggg cacccagaca 240

tatatctgca acgtgaatca caagccatca aatacaaaag tcgacaagaa agtg 294

<210> SEQ ID NO 109
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 109

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
50 55 60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
100 105 110

<210> SEQ ID NO 110
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

-continued

<400> SEQUENCE: 110

gcgccagaac tgctgggagg accaagcgtg ttcctgtttc cacccaagcc taaagacacc 60

ctgatgattt cccggactcc tgaggtcacc tgcgtggtcg tggacgtgtc tcacgaggac 120

cccgaagtca agttcaactg gtacgtggat ggcgtcgaag tgcataatgc caagaccaaa 180

ccccgggagg aacagtacaa ctctacctat agagtcgtga gtgtcctgac agtgctgcac 240

caggactggc tgaatgggaa ggagtataag tgtaaagtga gcaacaaagc cctgcccgcc 300

ccaatcgaaa aaacaatctc taaagcaaaa 330

<210> SEQ ID NO 111
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 111

Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr Pro Pro Ser Arg Asp
1 5 10 15

Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
20 25 30

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
35 40 45

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
50 55 60

Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
65 70 75 80

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
85 90 95

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
100 105

<210> SEQ ID NO 112
<211> LENGTH: 318
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 112

ggacagcctc gcgaaccaca ggtctacgtc tacccccat caagagatga actgacaaaa 60

aatcaggtct ctctgacatg cctggtcaaa ggattctacc cttccgacat cgccgtggag 120

tgggaaagta acggccagcc cgagaacaat tacaagacca cacccctgt cctggactct 180

gatgggagtt tcgctctggt gtcaaagctg accgtcgata aaagccggtg gcagcagggc 240

aatgtgttta gctgctccgt catgcacgaa gccctgcaca atcactacac acagaagtcc 300

ctgagcctga gccctggc 318

<210> SEQ ID NO 113
<211> LENGTH: 226
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

-continued

polypeptide

<400> SEQUENCE: 113

Tyr Pro Tyr Asp Val Pro Asp Tyr Ala Thr Gly Ser Asp Ile Gln Met
1 5 10 15

Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr
20 25 30

Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Ile Gly Val Ala Trp Tyr
35 40 45

Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ser Ala Ser
50 55 60

Tyr Arg Tyr Thr Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly
65 70 75 80

Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala
85 90 95

Thr Tyr Tyr Cys Gln Gln Tyr Tyr Ile Tyr Pro Tyr Thr Phe Gly Gln
100 105 110

Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe
115 120 125

Ile Phe Pro Pro Ser Asp Glu Glu Leu Lys Ser Gly Thr Ala Ser Val
130 135 140

Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp
145 150 155 160

Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Glu Glu Ser Val Thr
165 170 175

Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Glu
180 185 190

Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val
195 200 205

Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly
210 215 220

Glu Cys
225

<210> SEQ ID NO 114
<211> LENGTH: 678
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 114

tatccctacg atgtgcctga ctacgctact ggctccgata tccagatgac ccagtctcca 60

agctccctga gtgcatcagt gggggaccga gtcaccatca catgcaaggc ttcccaggat 120

gtgtctattg gagtcgcatg gtaccagcag aagccaggca aagcacccaa gctgctgatc 180

tacagcgcct cctaccggta tactggggtg ccttccagat tctctggcag tgggtcagga 240

accgacttta ctctgaccat ctctagtctg cagcccgagg atttcgccac ctactattgc 300

cagcagtact atatctaccc ttataccttt ggccagggga caaaagtgga gatcaagagg 360

acagtggccg ctccaagtgt cttcattttt ccccccttccg acgaagagct gaaaagtgga 420

actgcttcag tggtctgtct gctgaacaat ttctaccccc gcgaagccaa agtgcagtgg 480

-continued

aaggtcgata acgctctgca gagcggcaat tccgaggagt ctgtgacaga acaggacagt 540

aaagattcaa cttatagcct gtcaagcaca ctggagctgt ctaaggcaga ctacgagaag 600

cacaaagtgt atgcctgcga agtcacccat caggggctgt cctctcccgt gacaaagagc 660

tttaacagag gagagtgt 678

<210> SEQ ID NO 115
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 115

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Ile Gly
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Ile Tyr Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 116
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 116

gatatccaga tgacccagtc tccaagctcc ctgagtgcat cagtggggga ccgagtcacc 60

atcacatgca aggcttccca ggatgtgtct attggagtcg catggtacca gcagaagcca 120

ggcaaagcac ccaagctgct gatctacagc gcctcctacc ggtatactgg ggtgccttcc 180

agattctctg gcagtgggtc aggaaccgac tttactctga ccatctctag tctgcagccc 240

gaggatttcg ccacctacta ttgccagcag tactatatct acccttatac ctttggccag 300

gggacaaaag tggagatcaa g 321

<210> SEQ ID NO 117
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 117

Gln Asp Val Ser Ile Gly
1 5

-continued

<210> SEQ ID NO 118
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 118

caggatgtgt ctattgga 18

<210> SEQ ID NO 119
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 119

Gln Gln Tyr Tyr Ile Tyr Pro Tyr Thr
1 5

<210> SEQ ID NO 120
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 120

cagcagtact atatctaccc ttatacc 27

<210> SEQ ID NO 121
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 121

Ser Ala Ser
1

<210> SEQ ID NO 122
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 122

agcgcctcc 9

<210> SEQ ID NO 123
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

-continued

<400> SEQUENCE: 123

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
1 5 10 15

Glu Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
20 25 30

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
35 40 45

Ser Gly Asn Ser Glu Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
50 55 60

Thr Tyr Ser Leu Ser Ser Thr Leu Glu Leu Ser Lys Ala Asp Tyr Glu
65 70 75 80

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
85 90 95

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
100 105

<210> SEQ ID NO 124
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 124

aggacagtgg ccgctccaag tgtcttcatt tttccccctt ccgacgaaga gctgaaaagt 60

ggaactgctt cagtggtctg tctgctgaac aatttctacc cccgcgaagc caaagtgcag 120

tggaaggtcg ataacgctct gcagagcggc aattccgagg agtctgtgac agaacaggac 180

agtaaagatt caacttatag cctgtcaagc acactggagc tgtctaaggc agactacgag 240

aagcacaaag tgtatgcctg cgaagtcacc catcaggggc tgtcctctcc cgtgacaaag 300

agctttaaca gaggagagtg t 321

<210> SEQ ID NO 125
<211> LENGTH: 450
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 125

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr
20 25 30

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

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Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
    210                 215                 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225                 230                 235                 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                245                 250                 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            260                 265                 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        275                 280                 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
    290                 295                 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305                 310                 315                 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                325                 330                 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            340                 345                 350

Val Tyr Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
        355                 360                 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385                 390                 395                 400

Leu Asp Ser Asp Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp
                405                 410                 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            420                 425                 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        435                 440                 445

Gly Lys
    450
```

<210> SEQ ID NO 126
<211> LENGTH: 1350
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

-continued

polynucleotide

<400> SEQUENCE: 126

gaagtccagc tggtcgaaag cggaggagga ctggtgcagc caggagggtc tctgcgactg 60

agttgcgccg cttcaggctt caacatcaag gacacctaca ttcactgggt gcgccaggct 120

cctggaaaag gcctggagtg ggtggcacga atctatccaa ctaatggata cacccggtat 180

gcagacagcg tgaagggccg gttcaccatt agcgcagata catccaaaaa cactgcctac 240

ctgcagatga acagcctgcg agccgaagat actgctgtgt actattgcag tcggtgggga 300

ggcgacggct tctacgctat ggattattgg gggcagggaa ccctggtcac agtgagctcc 360

gcatctacaa aggggcctag tgtgtttcca ctggcccccc ctagtaaatc cacctctggg 420

ggaacagcag ccctgggatg tctggtgaag gactatttcc cagagcccgt cactgtgagt 480

tggaactcag gcgccctgac atccggggtc catacttttc ctgctgtgct gcagtcaagc 540

ggcctgtact ctctgtcctc tgtggtcacc gtgccaagtt caagcctggg gactcagacc 600

tatatctgca acgtgaatca caagccaagc aatacaaaag tcgacaagaa agtggaaccc 660

aagagctgtg ataaaacaca tacttgcccc ccttgtcctg caccagagct gctgggagga 720

ccatccgtgt tcctgtttcc acccaagcct aaagacaccc tgatgatttc caggactcca 780

gaagtcacct gcgtggtcgt ggacgtgtct cacgaggacc ccgaagtcaa gttcaactgg 840

tacgtggatg gcgtcgaggt gcataatgcc aagacaaaac ccagggagga acagtacaac 900

tcaacttatc gcgtcgtgag cgtcctgacc gtgctgcacc aggactggct gaacggcaag 960

gagtataagt gcaaagtgag caataaggct ctgcccgcac ctatcgagaa aaccattagc 1020

aaggccaaag ggcagcctag agaaccacag gtctacgtgt atcctccaag cagggacgag 1080

ctgaccaaga accaggtctc cctgacatgt ctggtgaaag ggttttaccc cagtgatatc 1140

gctgtggagt gggaatcaaa tggacagcct gaaaacaatt ataagaccac acccccctgtg 1200

ctggacagcg atggcagctt cgctctggtc tccaagctga ctgtggataa atctcggtgg 1260

cagcagggca acgtctttag ttgttcagtg atgcatgagg cactgcacaa tcattacacc 1320

cagaagagcc tgtccctgtc tcccggcaaa 1350

<210> SEQ ID NO 127
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 127

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr
20 25 30

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

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Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 128
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 128

gaagtccagc tggtcgaaag cggaggagga ctggtgcagc caggagggtc tctgcgactg 60

agttgcgccg cttcaggctt caacatcaag gacacctaca ttcactgggt gcgccaggct 120

cctggaaaag gcctggagtg ggtggcacga atctatccaa ctaatggata cacccggtat 180

gcagacagcg tgaagggccg gttcaccatt agcgcagata catccaaaaa cactgcctac 240

ctgcagatga acagcctgcg agccgaagat actgctgtgt actattgcag tcggtgggga 300

ggcgacggct tctacgctat ggattattgg gggcagggaa ccctggtcac agtgagctcc 360

<210> SEQ ID NO 129
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 129

Gly Phe Asn Ile Lys Asp Thr Tyr
1 5

<210> SEQ ID NO 130
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 130

ggcttcaaca tcaaggacac ctac 24

<210> SEQ ID NO 131
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 131

Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr
1 5 10

<210> SEQ ID NO 132
<211> LENGTH: 39

-continued

<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 132

agtcggtggg gaggcgacgg cttctacgct atggattat 39

<210> SEQ ID NO 133
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 133

Ile Tyr Pro Thr Asn Gly Tyr Thr
1 5

<210> SEQ ID NO 134
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 134

atctatccaa ctaatggata cacc 24

<210> SEQ ID NO 135
<211> LENGTH: 98
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 135

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val

<210> SEQ ID NO 136
<211> LENGTH: 294
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

-continued

<400> SEQUENCE: 136

gcatctacaa aggggcctag tgtgtttcca ctggcccct ctagtaaatc cacctctggg 60

ggaacagcag ccctgggatg tctggtgaag gactatttcc cagagcccgt cactgtgagt 120

tggaactcag gcgccctgac atccggggtc catacttttc ctgctgtgct gcagtcaagc 180

ggcctgtact ctctgtcctc tgtggtcacc gtgccaagtt caagcctggg gactcagacc 240

tatatctgca acgtgaatca caagccaagc aatacaaaag tcgacaagaa agtg 294

<210> SEQ ID NO 137
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 137

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
50 55 60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
100 105 110

<210> SEQ ID NO 138
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 138

gcaccagagc tgctgggagg accatccgtg ttcctgtttc cacccaagcc taaagacacc 60

ctgatgattt ccaggactcc agaagtcacc tgcgtggtcg tggacgtgtc tcacgaggac 120

cccgaagtca agttcaactg gtacgtggat ggcgtcgagg tgcataatgc caagacaaaa 180

cccagggagg aacagtacaa ctcaacttat cgcgtcgtga gcgtcctgac cgtgctgcac 240

caggactggc tgaacggcaa ggagtataag tgcaaagtga gcaataaggc tctgcccgca 300

cctatcgaga aaaccattag caaggccaaa 330

<210> SEQ ID NO 139
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

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<400> SEQUENCE: 139

Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr Pro Pro Ser Arg Asp
1 5 10 15

Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
20 25 30

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
35 40 45

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
50 55 60

Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
65 70 75 80

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
85 90 95

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
100 105

<210> SEQ ID NO 140
<211> LENGTH: 318
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 140

gggcagccta gagaaccaca ggtctacgtg tatcctccaa gcagggacga gctgaccaag 60

aaccaggtct ccctgacatg tctggtgaaa gggttttacc ccagtgatat cgctgtggag 120

tgggaatcaa atggacagcc tgaaaacaat tataagacca cacccctgt gctggacagc 180

gatggcagct tcgctctggt ctccaagctg actgtggata aatctcggtg gcagcagggc 240

aacgtcttta gttgttcagt gatgcatgag gcactgcaca atcattacac ccagaagagc 300

ctgtccctgt ctcccggc 318

<210> SEQ ID NO 141
<211> LENGTH: 232
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 141

Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
1 5 10 15

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
20 25 30

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
35 40 45

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
50 55 60

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
65 70 75 80

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
85 90 95

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Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
            100                 105                 110

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
        115                 120                 125

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
    130                 135                 140

Lys Asn Gln Val Ser Leu Ile Cys Leu Val Lys Gly Phe Tyr Pro Ser
145                 150                 155                 160

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Arg Tyr
                165                 170                 175

Met Thr Trp Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
            180                 185                 190

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
        195                 200                 205

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
    210                 215                 220

Ser Leu Ser Leu Ser Pro Gly Lys
225                 230


<210> SEQ ID NO 142
<211> LENGTH: 696
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide

<400> SEQUENCE: 142

gagcccaaga gcagcgataa gacccacacc tgccctccct gtccagctcc agaactgctg     60

ggaggaccta gcgtgttcct gtttcccccc aagccaaaag acactctgat gatttccagg    120

actcccgagg tgacctgcgt ggtggtggac gtgtctcacg aggaccccga agtgaagttc    180

aactggtacg tggatggcgt ggaagtgcat aatgctaaga caaaaccaag agaggaacag    240

tacaactcca cttatcgcgt cgtgagcgtg ctgaccgtgc tgcaccagga ctggctgaac    300

gggaaggagt ataagtgcaa agtcagtaat aaggccctgc ctgctccaat cgaaaaaacc    360

atctctaagg ccaaaggcca gccaagggag ccccaggtgt acacactgcc acccagcaga    420

gacgaactga ccaagaacca ggtgtccctg atctgtctgg tgaaaggctt ctatcctagt    480

gatattgctg tggagtggga atcaaatgga cagccagaga acagatacat gacctggcct    540

ccagtgctgg acagcgatgg cagcttcttc ctgtattcca agctgacagt ggataaatct    600

cgatggcagc aggggaacgt gtttagttgt tcagtgatgc atgaagccct gcacaatcat    660

tacactcaga agagcctgtc cctgtctccc ggcaaa                               696


<210> SEQ ID NO 143
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 143

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                   10                  15
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Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
            100                 105                 110


<210> SEQ ID NO 144
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide

<400> SEQUENCE: 144

gctccagaac tgctgggagg acctagcgtg ttcctgtttc cccctaagcc aaaagacact     60

ctgatgattt ccaggactcc cgaggtgacc tgcgtggtgg tggacgtgtc tcacgaggac    120

cccgaagtga agttcaactg gtacgtggat ggcgtggaag tgcataatgc taagacaaaa    180

ccaagagagg aacagtacaa ctccacttat cgcgtcgtga gcgtgctgac cgtgctgcac    240

caggactggc tgaacgggaa ggagtataag tgcaaagtca gtaataaggc cctgcctgct    300

ccaatcgaaa aaaccatctc taaggccaaa                                     330


<210> SEQ ID NO 145
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 145

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
1               5                   10                  15

Glu Leu Thr Lys Asn Gln Val Ser Leu Ile Cys Leu Val Lys Gly Phe
            20                  25                  30

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
        35                  40                  45

Asn Arg Tyr Met Thr Trp Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
    50                  55                  60

Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
65                  70                  75                  80

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
                85                  90                  95

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
            100                 105


<210> SEQ ID NO 146
<211> LENGTH: 318
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 146

ggccagccaa gggagcccca ggtgtacaca ctgccaccca gcagagacga actgaccaag 60

aaccaggtgt ccctgatctg tctggtgaaa ggcttctatc ctagtgatat tgctgtggag 120

tgggaatcaa atggacagcc agagaacaga tacatgacct ggcctccagt gctggacagc 180

gatggcagct tcttcctgta ttccaagctg acagtggata aatctcgatg gcagcagggg 240

aacgtgttta gttgttcagt gatgcatgaa gccctgcaca atcattacac tcagaagagc 300

ctgtccctgt ctcccggc 318

<210> SEQ ID NO 147
<211> LENGTH: 481
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 147

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Asn Thr Ala
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Pro
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Gly Gly Ser Gly Gly
100 105 110

Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Glu
115 120 125

Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser
130 135 140

Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr Tyr
145 150 155 160

Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala
165 170 175

Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val Lys
180 185 190

Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr Leu
195 200 205

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ser
210 215 220

Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln Gly
225 230 235 240

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Thr Leu Val Thr Val Ser Ser Ala Ala Glu Pro Lys Ser Ser Asp Lys
                245                 250                 255

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
            260                 265                 270

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
        275                 280                 285

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
    290                 295                 300

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
305                 310                 315                 320

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
                325                 330                 335

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
            340                 345                 350

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
        355                 360                 365

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
    370                 375                 380

Tyr Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
385                 390                 395                 400

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
                405                 410                 415

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
            420                 425                 430

Asp Glu Asp Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp Lys
        435                 440                 445

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
    450                 455                 460

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
465                 470                 475                 480

Lys
```

<210> SEQ ID NO 148
<211> LENGTH: 1443
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 148

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gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc     60

atcacttgcc gggcaagtca ggacgttaac accgctgtag cttggtatca gcagaaacca    120

gggaaagccc ctaagctcct gatctattct gcatcctttt tgtacagtgg ggtcccatca    180

aggttcagtg gcagtcgatc tgggacagat ttcactctca ccatcagcag tctgcaacct    240

gaagattttg caacttacta ctgtcaacag cattacacta ccccacccac tttcggccaa    300

gggaccaaag tggagatcaa aggtggttct ggtggtggtt ctggtggtgg ttctggtggt    360

ggttctggtg gtggttctgg tgaagtgcag ctggtggagt ctgggggagg cttggtacag    420

cctggcgggt ccctgagact ctcctgtgca gcctctggat tcaacattaa agatacttat    480

atccactggg tccggcaagc tccagggaag ggcctggagt gggtcgcacg tatttatccc    540
```

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acaaatggtt acacacggta tgcggactct gtgaagggcc gattcaccat ctccgcagac 600

acttccaaga acaccgcgta tctgcaaatg aacagtctga gagctgagga cacggccgtt 660

tattactgtt caagatgggg cggagacggt ttctacgcta tggactactg gggccaaggg 720

accctggtca ccgtctcctc agccgccgag cccaagagca gcgataagac ccacacctgc 780

cctccctgtc cagctccaga actgctggga ggacctagcg tgttcctgtt tccccctaag 840

ccaaaagaca ctctgatgat ttccaggact cccgaggtga cctgcgtggt ggtggacgtg 900

tctcacgagg accccgaagt gaagttcaac tggtacgtgg atggcgtgga agtgcataat 960

gctaagacaa aaccaagaga ggaacagtac aactccactt atcgcgtcgt gagcgtgctg 1020

accgtgctgc accaggactg gctgaacggg aaggagtata agtgcaaagt cagtaataag 1080

gccctgcctg ctccaatcga aaaaaccatc tctaaggcca aaggccagcc aagggagccc 1140

caggtgtaca catacccacc cagcagagac gaactgacca agaaccaggt gtccctgaca 1200

tgtctggtga aaggcttcta tcctagtgat attgctgtgg agtgggaatc aaatggacag 1260

ccagagaaca attacaagac cacacctcca gtgctggacg aggatggcag cttcgccctg 1320

gtgtccaagc tgacagtgga taaatctcga tggcagcagg ggaacgtgtt tagttgttca 1380

gtgatgcatg aagccctgca caatcattac actcagaaga gcctgtccct gtctcccggc 1440

aaa 1443

<210> SEQ ID NO 149
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 149

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Asn Thr Ala
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Pro
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 150
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 150

gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

-continued

atcacttgcc gggcaagtca ggacgttaac accgctgtag cttggtatca gcagaaacca 120

gggaaagccc ctaagctcct gatctattct gcatcctttt tgtacagtgg ggtcccatca 180

aggttcagtg gcagtcgatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240

gaagattttg caacttacta ctgtcaacag cattacacta ccccacccac tttcggccaa 300

gggaccaaag tggagatcaa a 321

<210> SEQ ID NO 151
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 151

Gln Asp Val Asn Thr Ala
1 5

<210> SEQ ID NO 152
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 152

caggacgtta acaccgct 18

<210> SEQ ID NO 153
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 153

Gln Gln His Tyr Thr Thr Pro Pro Thr
1 5

<210> SEQ ID NO 154
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 154

caacagcatt acactacccc acccact 27

<210> SEQ ID NO 155
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 155

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Ser Ala Ser
1

<210> SEQ ID NO 156
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 156

tctgcatcc 9

<210> SEQ ID NO 157
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 157

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr
20 25 30

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 158
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 158

gaagtgcagc tggtggagtc tgggggaggc ttggtacagc ctggcgggtc cctgagactc 60

tcctgtgcag cctctggatt caacattaaa gatacttata tccactgggt ccggcaagct 120

ccagggaagg gcctggagtg ggtcgcacgt atttatccca caaatggtta cacacggtat 180

gcggactctg tgaagggccg attcaccatc tccgcagaca cttccaagaa caccgcgtat 240

ctgcaaatga acagtctgag agctgaggac acggccgttt attactgttc aagatggggc 300

ggagacggtt tctacgctat ggactactgg ggccaaggga ccctggtcac cgtctcctca 360

<210> SEQ ID NO 159

-continued

<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 159

Gly Phe Asn Ile Lys Asp Thr Tyr
1 5

<210> SEQ ID NO 160
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 160

ggattcaaca ttaaagatac ttat 24

<210> SEQ ID NO 161
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 161

Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr
1 5 10

<210> SEQ ID NO 162
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 162

tcaagatggg gcggagacgg tttctacgct atggactac 39

<210> SEQ ID NO 163
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 163

Ile Tyr Pro Thr Asn Gly Tyr Thr
1 5

<210> SEQ ID NO 164
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 164

-continued

atttatccca caaatggtta caca 24

<210> SEQ ID NO 165
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 165

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
50 55 60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
100 105 110

<210> SEQ ID NO 166
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 166

gctccagaac tgctgggagg acctagcgtg ttcctgtttc cccctaagcc aaaagacact 60

ctgatgattt ccaggactcc cgaggtgacc tgcgtggtgg tggacgtgtc tcacgaggac 120

cccgaagtga agttcaactg gtacgtggat ggcgtggaag tgcataatgc taagacaaaa 180

ccaagagagg aacagtacaa ctccacttat cgcgtcgtga gcgtgctgac cgtgctgcac 240

caggactggc tgaacgggaa ggagtataag tgcaaagtca gtaataaggc cctgcctgct 300

ccaatcgaaa aaaccatctc taaggccaaa 330

<210> SEQ ID NO 167
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 167

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Tyr Pro Pro Ser Arg Asp
1 5 10 15

Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
20 25 30

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu

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        35                  40                  45

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Glu Asp Gly Ser Phe
    50                  55                  60

Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
65                  70                  75                  80

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
                85                  90                  95

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
            100                 105


<210> SEQ ID NO 168
<211> LENGTH: 318
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide

<400> SEQUENCE: 168

ggccagccaa gggagcccca ggtgtacaca tacccaccca gcagagacga actgaccaag     60

aaccaggtgt ccctgacatg tctggtgaaa ggcttctatc ctagtgatat tgctgtggag    120

tgggaatcaa atggacagcc agagaacaat tacaagacca cacctccagt gctggacgag    180

gatggcagct tcgccctggt gtccaagctg acagtggata aatctcgatg gcagcagggg    240

aacgtgttta gttgttcagt gatgcatgaa gccctgcaca atcattacac tcagaagagc    300

ctgtccctgt ctcccggc                                                  318


<210> SEQ ID NO 169
<211> LENGTH: 481
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 169

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Asn Thr Ala
            20                  25                  30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Arg Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Pro
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Gly Gly Ser Gly Gly
            100                 105                 110

Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Glu
        115                 120                 125

Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser
    130                 135                 140

Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr Tyr
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145                 150                 155                 160

Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala
                165                 170                 175

Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val Lys
            180                 185                 190

Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr Leu
        195                 200                 205

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ser
    210                 215                 220

Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln Gly
225                 230                 235                 240

Thr Leu Val Thr Val Ser Ser Ala Ala Glu Pro Lys Ser Ser Asp Lys
                245                 250                 255

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
            260                 265                 270

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
        275                 280                 285

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
    290                 295                 300

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
305                 310                 315                 320

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
                325                 330                 335

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
            340                 345                 350

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
        355                 360                 365

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
    370                 375                 380

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Ile
385                 390                 395                 400

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
                405                 410                 415

Ser Asn Gly Gln Pro Glu Asn Arg Tyr Met Thr Trp Pro Pro Val Leu
            420                 425                 430

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
        435                 440                 445

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
    450                 455                 460

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
465                 470                 475                 480

Lys
```

<210> SEQ ID NO 170
<211> LENGTH: 1443
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 170

```
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc     60
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-continued

atcacttgcc gggcaagtca ggacgttaac accgctgtag cttggtatca gcagaaacca 120

gggaaagccc ctaagctcct gatctattct gcatcctttt tgtacagtgg ggtcccatca 180

aggttcagtg gcagtcgatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240

gaagattttg caacttacta ctgtcaacag cattacacta ccccacccac tttcggccaa 300

gggaccaaag tggagatcaa aggtggttct ggtggtggtt ctggtggtgg ttctggtggt 360

ggttctggtg gtggttctgg tgaagtgcag ctggtggagt ctgggggagg cttggtacag 420

cctggcgggt ccctgagact ctcctgtgca gcctctggat tcaacattaa agatacttat 480

atccactggg tccggcaagc tccagggaag ggcctggagt gggtcgcacg tatttatccc 540

acaaatggtt acacacggta tgcggactct gtgaagggcc gattcaccat ctccgcagac 600

acttccaaga acaccgcgta tctgcaaatg aacagtctga gagctgagga cacggccgtt 660

tattactgtt caagatgggg cggagacggt ttctacgcta tggactactg gggccaaggg 720

accctggtca ccgtctcctc agccgccgag cccaagagca gcgataagac ccacacctgc 780

cctccctgtc cagctccaga actgctggga ggacctagcg tgttcctgtt tccccctaag 840

ccaaaagaca ctctgatgat ttccaggact cccgaggtga cctgcgtggt ggtggacgtg 900

tctcacgagg accccgaagt gaagttcaac tggtacgtgg atggcgtgga agtgcataat 960

gctaagacaa aaccaagaga ggaacagtac aactccactt atcgcgtcgt gagcgtgctg 1020

accgtgctgc accaggactg gctgaacggg aaggagtata agtgcaaagt cagtaataag 1080

gccctgcctg ctccaatcga aaaaaccatc tctaaggcca aaggccagcc aagggagccc 1140

caggtgtaca cactgccacc cagcagagac gaactgacca agaaccaggt gtccctgatc 1200

tgtctggtga aaggcttcta tcctagtgat attgctgtgg agtgggaatc aaatggacag 1260

ccagagaaca gatacatgac ctggcctcca gtgctggaca gcgatggcag cttcttcctg 1320

tattccaagc tgacagtgga taaatctcga tggcagcagg ggaacgtgtt tagttgttca 1380

gtgatgcatg aagccctgca caatcattac actcagaaga gcctgtccct gtctcccggc 1440

aaa 1443

<210> SEQ ID NO 171
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 171

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Asn Thr Ala
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Pro

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85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 172
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 172

gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggcaagtca ggacgttaac accgctgtag cttggtatca gcagaaacca 120

gggaaagccc ctaagctcct gatctattct gcatcctttt tgtacagtgg ggtcccatca 180

aggttcagtg gcagtcgatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240

gaagattttg caacttacta ctgtcaacag cattacacta ccccacccac tttcggccaa 300

gggaccaaag tggagatcaa a 321

<210> SEQ ID NO 173
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 173

Gln Asp Val Asn Thr Ala
1 5

<210> SEQ ID NO 174
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 174

caggacgtta acaccgct 18

<210> SEQ ID NO 175
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 175

Gln Gln His Tyr Thr Thr Pro Pro Thr
1 5

<210> SEQ ID NO 176
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

-continued

oligonucleotide

<400> SEQUENCE: 176

caacagcatt acactacccc acccact 27

<210> SEQ ID NO 177
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 177

Ser Ala Ser
1

<210> SEQ ID NO 178
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 178

tctgcatcc 9

<210> SEQ ID NO 179
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 179

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr
20 25 30

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 180
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

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<400> SEQUENCE: 180

gaagtgcagc tggtggagtc tgggggaggc ttggtacagc ctggcgggtc cctgagactc 60

tcctgtgcag cctctggatt caacattaaa gatacttata tccactgggt ccggcaagct 120

ccagggaagg gcctggagtg ggtcgcacgt atttatccca caaatggtta cacacggtat 180

gcggactctg tgaagggccg attcaccatc tccgcagaca cttccaagaa caccgcgtat 240

ctgcaaatga acagtctgag agctgaggac acggccgttt attactgttc aagatggggc 300

ggagacggtt tctacgctat ggactactgg ggccaaggga ccctggtcac cgtctcctca 360

<210> SEQ ID NO 181
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 181

Gly Phe Asn Ile Lys Asp Thr Tyr
1 5

<210> SEQ ID NO 182
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 182

ggattcaaca ttaaagatac ttat 24

<210> SEQ ID NO 183
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 183

Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr
1 5 10

<210> SEQ ID NO 184
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 184

tcaagatggg gcggagacgg tttctacgct atggactac 39

<210> SEQ ID NO 185
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

-continued

peptide

<400> SEQUENCE: 185

Ile Tyr Pro Thr Asn Gly Tyr Thr
1 5

<210> SEQ ID NO 186
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 186

atttatccca caaatggtta caca 24

<210> SEQ ID NO 187
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 187

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
50 55 60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
100 105 110

<210> SEQ ID NO 188
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 188

gctccagaac tgctgggagg acctagcgtg ttcctgtttc cccctaagcc aaaagacact 60

ctgatgattt ccaggactcc cgaggtgacc tgcgtggtgg tggacgtgtc tcacgaggac 120

cccgaagtga agttcaactg gtacgtggat ggcgtggaag tgcataatgc taagacaaaa 180

ccaagagagg aacagtacaa ctccacttat cgcgtcgtga gcgtgctgac cgtgctgcac 240

caggactggc tgaacgggaa ggagtataag tgcaaagtca gtaataaggc cctgcctgct 300

ccaatcgaaa aaaccatctc taaggccaaa 330

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<210> SEQ ID NO 189
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 189

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
1 5 10 15

Glu Leu Thr Lys Asn Gln Val Ser Leu Ile Cys Leu Val Lys Gly Phe
20 25 30

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
35 40 45

Asn Arg Tyr Met Thr Trp Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
50 55 60

Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
65 70 75 80

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
85 90 95

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
100 105

<210> SEQ ID NO 190
<211> LENGTH: 318
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 190

ggccagccaa gggagcccca ggtgtacaca ctgccaccca gcagagacga actgaccaag 60

aaccaggtgt ccctgatctg tctggtgaaa ggcttctatc ctagtgatat tgctgtggag 120

tgggaatcaa atggacagcc agagaacaga tacatgacct ggcctccagt gctggacagc 180

gatggcagct tcttcctgta ttccaagctg acagtggata aatctcgatg gcagcagggg 240

aacgtgttta gttgttcagt gatgcatgaa gccctgcaca atcattacac tcagaagagc 300

ctgtccctgt ctcccggc 318

<210> SEQ ID NO 191
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 191

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Asn Thr Ala
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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Ser Arg Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Pro
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
    210
```

<210> SEQ ID NO 192
<211> LENGTH: 642
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 192

```
gatattcaga tgacccagtc ccctagctcc ctgtccgctt ctgtgggcga cagggtcact     60

atcacctgcc gcgcatctca ggatgtgaac accgcagtcg cctggtacca gcagaagcct    120

gggaaagctc caaagctgct gatctacagt gcatcattcc tgtattcagg agtgcccagc    180

cggtttagcg gcagcagatc tggcaccgac ttcacactga ctatctctag tctgcagcct    240

gaggattttg ccacatacta ttgccagcag cactatacca cacccctac tttcggccag    300

gggaccaaag tggagatcaa gcgaactgtg gccgctccaa gtgtcttcat ttttccaccc    360

agcgacgaac agctgaaatc cggcacagct tctgtggtct gtctgctgaa caacttctac    420

cccagagagg ccaaagtgca gtggaaggtc gataacgctc tgcagagtgg caacagccag    480

gagagcgtga cagaacagga ctccaaagat tctacttata gtctgtcaag caccctgaca    540

ctgagcaagg cagactacga aaagcataaa gtgtatgcct gtgaggtgac ccatcagggg    600

ctgtcttctc ccgtgaccaa gtctttcaac cgaggcgaat gt                       642
```

<210> SEQ ID NO 193
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 193

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
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1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Asn Thr Ala
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Pro
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 194
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 194

gatattcaga tgacccagtc ccctagctcc ctgtccgctt ctgtgggcga cagggtcact 60

atcacctgcc gcgcatctca ggatgtgaac accgcagtcg cctggtacca gcagaagcct 120

gggaaagctc caaagctgct gatctacagt gcatcattcc tgtattcagg agtgcccagc 180

cggtttagcg gcagcagatc tggcaccgac ttcacactga ctatctctag tctgcagcct 240

gaggattttg ccacatacta ttgccagcag cactatacca cacccctac tttcggccag 300

gggaccaaag tggagatcaa g 321

<210> SEQ ID NO 195
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 195

Gln Asp Val Asn Thr Ala
1 5

<210> SEQ ID NO 196
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 196

caggatgtga acaccgca 18

<210> SEQ ID NO 197
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

-continued

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 197

Gln Gln His Tyr Thr Thr Pro Pro Thr
1 5

<210> SEQ ID NO 198
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 198

cagcagcact ataccacacc ccctact 27

<210> SEQ ID NO 199
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 199

Ser Ala Ser
1

<210> SEQ ID NO 200
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 200

agtgcatca 9

<210> SEQ ID NO 201
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 201

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
1 5 10 15

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
20 25 30

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
35 40 45

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
50 55 60

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
65 70 75 80

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
85 90 95

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Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
100 105

<210> SEQ ID NO 202
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 202

cgaactgtgg ccgctccaag tgtcttcatt tttccaccca gcgacgaaca gctgaaatcc 60

ggcacagctt ctgtggtctg tctgctgaac aacttctacc ccagagaggc caaagtgcag 120

tggaaggtcg ataacgctct gcagagtggc aacagccagg agagcgtgac agaacaggac 180

tccaaagatt ctacttatag tctgtcaagc accctgacac tgagcaaggc agactacgaa 240

aagcataaag tgtatgcctg tgaggtgacc catcaggggc tgtcttctcc cgtgaccaag 300

tctttcaacc gaggcgaatg t 321

<210> SEQ ID NO 203
<211> LENGTH: 448
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 203

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Asp Tyr
20 25 30

Thr Met Asp Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asp Val Asn Pro Asn Ser Gly Gly Ser Ile Tyr Asn Gln Arg Phe
50 55 60

Lys Gly Arg Phe Thr Leu Ser Val Asp Arg Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asn Leu Gly Pro Ser Phe Tyr Phe Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

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Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
    210                 215                 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
            260                 265                 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
    290                 295                 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305                 310                 315                 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
                325                 330                 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val
            340                 345                 350

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Leu
        355                 360                 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
    370                 375                 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val Leu
385                 390                 395                 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
                405                 410                 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
            420                 425                 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440                 445


<210> SEQ ID NO 204
<211> LENGTH: 1344
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide

<400> SEQUENCE: 204

gaagtgcagc tggtcgaatc tggaggagga ctggtgcagc caggagggtc cctgcgcctg     60

tcttgcgccg ctagtggctt cacttttacc gactacacca tggattgggt gcgacaggca    120

cctggaaagg gcctggagtg ggtcgccgat gtgaacccaa atagcggagg ctccatctac    180

aaccagcggt tcaagggccg gttcaccctg tcagtggacc ggagcaaaaa caccctgtat    240

ctgcagatga atagcctgcg agccgaagat actgctgtgt actattgcgc ccggaatctg    300

gggccctcct tctactttga ctattggggg cagggaactc tggtcaccgt gagctccgcc    360

tccaccaagg gaccttctgt gttcccactg gctccctcta gtaaatccac atctggggga    420

actgcagccc tgggctgtct ggtgaaggac tacttcccag agcccgtcac agtgtcttgg    480

aacagtggcg ctctgacttc tggggtccac acctttcctg cagtgctgca gtcaagcggg    540

ctgtacagcc tgtcctctgt ggtcaccgtg ccaagttcaa gcctgggaac acagacttat    600
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atctgcaacg tgaatcacaa gccatccaat acaaaagtcg acaagaaagt ggaacccaag 660

tcttgtgata aaacccatac atgccccct tgtcctgcac cagagctgct gggaggacca 720

agcgtgttcc tgtttccacc caagcctaaa gatacactga tgattagtag gaccccagaa 780

gtcacatgcg tggtcgtgga cgtgagccac gaggaccccg aagtcaagtt taactggtac 840

gtggacggcg tcgaggtgca taatgccaag actaaaccca gggaggaaca gtacaacagt 900

acctatcgcg tcgtgtcagt cctgacagtg ctgcatcagg attggctgaa cgggaaagag 960

tataagtgca aagtgagcaa taaggctctg cccgcaccta tcgagaaaac aatttccaag 1020

gcaaaaggac agcctagaga accacaggtg tacgtgctgc ctccatcaag ggatgagctg 1080

acaaagaacc aggtcagcct gctgtgtctg gtgaaaggat tctatccctc tgacattgct 1140

gtggagtggg aaagtaatgg ccagcctgag aacaattacc tgacctggcc ccctgtgctg 1200

gactcagatg gcagcttctt tctgtatagc aagctgaccg tcgacaaatc ccggtggcag 1260

caggggaatg tgtttagttg ttcagtcatg cacgaggcac tgcacaacca ttacacccag 1320

aagtcactgt cactgtcacc aggg 1344

<210> SEQ ID NO 205
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 205

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Asp Tyr
20 25 30

Thr Met Asp Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asp Val Asn Pro Asn Ser Gly Gly Ser Ile Tyr Asn Gln Arg Phe
50 55 60

Lys Gly Arg Phe Thr Leu Ser Val Asp Arg Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asn Leu Gly Pro Ser Phe Tyr Phe Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> SEQ ID NO 206
<211> LENGTH: 357
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 206

gaagtgcagc tggtcgaatc tggaggagga ctggtgcagc caggagggtc cctgcgcctg 60

tcttgcgccg ctagtggctt cacttttacc gactacacca tggattgggt gcgacaggca 120

-continued

cctggaaagg gcctggagtg ggtcgccgat gtgaacccaa atagcggagg ctccatctac 180

aaccagcggt tcaagggccg gttcaccctg tcagtggacc ggagcaaaaa caccctgtat 240

ctgcagatga atagcctgcg agccgaagat actgctgtgt actattgcgc ccggaatctg 300

gggccctcct tctactttga ctattggggg cagggaactc tggtcaccgt gagctcc 357

<210> SEQ ID NO 207
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 207

Gly Phe Thr Phe Thr Asp Tyr Thr
1 5

<210> SEQ ID NO 208
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 208

ggcttcactt ttaccgacta cacc 24

<210> SEQ ID NO 209
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 209

Ala Arg Asn Leu Gly Pro Ser Phe Tyr Phe Asp Tyr
1 5 10

<210> SEQ ID NO 210
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 210

gcccggaatc tggggccctc cttctacttt gactat 36

<210> SEQ ID NO 211
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 211

Val Asn Pro Asn Ser Gly Gly Ser
1 5

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<210> SEQ ID NO 212
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 212

gtgaacccaa atagcggagg ctcc 24

<210> SEQ ID NO 213
<211> LENGTH: 98
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 213

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val

<210> SEQ ID NO 214
<211> LENGTH: 294
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 214

gcctccacca agggaccttc tgtgttccca ctggctccct ctagtaaatc cacatctggg 60

ggaactgcag ccctgggctg tctggtgaag gactacttcc cagagcccgt cacagtgtct 120

tggaacagtg gcgctctgac ttctggggtc cacacctttc ctgcagtgct gcagtcaagc 180

gggctgtaca gcctgtcctc tgtggtcacc gtgccaagtt caagcctggg aacacagact 240

tatatctgca acgtgaatca caagccatcc aatacaaaag tcgacaagaa agtg 294

<210> SEQ ID NO 215
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 215

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Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
50 55 60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
100 105 110

<210> SEQ ID NO 216
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 216

gcaccagagc tgctgggagg accaagcgtg ttcctgtttc cacccaagcc taaagataca 60

ctgatgatta gtaggacccc agaagtcaca tgcgtggtcg tggacgtgag ccacgaggac 120

cccgaagtca agtttaactg gtacgtggac ggcgtcgagg tgcataatgc caagactaaa 180

cccagggagg aacagtacaa cagtacctat cgcgtcgtgt cagtcctgac agtgctgcat 240

caggattggc tgaacgggaa agagtataag tgcaaagtga gcaataaggc tctgcccgca 300

cctatcgaga aaacaatttc caaggcaaaa 330

<210> SEQ ID NO 217
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 217

Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Leu Pro Pro Ser Arg Asp
1 5 10 15

Glu Leu Thr Lys Asn Gln Val Ser Leu Leu Cys Leu Val Lys Gly Phe
20 25 30

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
35 40 45

Asn Asn Tyr Leu Thr Trp Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
50 55 60

Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
65 70 75 80

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
85 90 95

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
100 105

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<210> SEQ ID NO 218
<211> LENGTH: 318
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 218

ggacagccta gagaaccaca ggtgtacgtg ctgcctccat caagggatga gctgacaaag 60

aaccaggtca gcctgctgtg tctggtgaaa ggattctatc cctctgacat tgctgtggag 120

tgggaaagta atggccagcc tgagaacaat tacctgacct ggccccctgt gctggactca 180

gatggcagct tctttctgta tagcaagctg accgtcgaca aatcccggtg gcagcagggg 240

aatgtgttta gttgttcagt catgcacgag gcactgcaca accattacac ccagaagtca 300

ctgtcactgt caccaggg 318

<210> SEQ ID NO 219
<211> LENGTH: 448
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 219

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Asp Tyr
20 25 30

Thr Met Asp Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asp Val Asn Pro Asn Ser Gly Gly Ser Ile Tyr Asn Gln Arg Phe
50 55 60

Lys Gly Arg Phe Thr Leu Ser Val Asp Arg Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asn Leu Gly Pro Ser Phe Tyr Phe Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
210 215 220

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Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
            260                 265                 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
    290                 295                 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305                 310                 315                 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
                325                 330                 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val
            340                 345                 350

Tyr Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
        355                 360                 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
    370                 375                 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385                 390                 395                 400

Asp Ser Asp Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp Lys
                405                 410                 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
            420                 425                 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440                 445


<210> SEQ ID NO 220
<211> LENGTH: 1344
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide

<400> SEQUENCE: 220

gaagtgcagc tggtcgaatc tggaggagga ctggtgcagc caggagggtc cctgcgcctg     60

tcttgcgccg ctagtggctt cacttttacc gactacacca tggattgggt gcgacaggca    120

cctggaaagg gcctggagtg ggtcgccgat gtgaacccaa atagcggagg ctccatctac    180

aaccagcggt tcaagggccg gttcaccctg tcagtggacc ggagcaaaaa caccctgtat    240

ctgcagatga atagcctgcg agccgaagat actgctgtgt actattgcgc ccggaatctg    300

gggccctcct tctactttga ctattggggg cagggaactc tggtcaccgt gagctccgcc    360

tccaccaagg gaccttctgt gttcccactg gctccctcta gtaaatccac atctggggga    420

actgcagccc tgggctgtct ggtgaaggac tacttcccag agcccgtcac agtgtcttgg    480

aacagtggcg ctctgacttc tggggtccac acctttcctg cagtgctgca gtcaagcggg    540

ctgtacagcc tgtcctctgt ggtcaccgtg ccaagttcaa gcctgggaac acagacttat    600

atctgcaacg tgaatcacaa gccatccaat acaaaagtcg acaagaaagt ggaacccaag    660
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tcttgtgata aaacccatac atgcccccct tgtcctgcac cagagctgct gggaggacca 720

agcgtgttcc tgtttccacc caagcctaaa gatacactga tgattagtag gaccccagaa 780

gtcacatgcg tggtcgtgga cgtgagccac gaggaccccg aagtcaagtt taactggtac 840

gtggacggcg tcgaggtgca taatgccaag actaaaccca gggaggaaca gtacaacagt 900

acctatcgcg tcgtgtcagt cctgacagtg ctgcatcagg attggctgaa cgggaaagag 960

tataagtgca aagtgagcaa taaggctctg cccgcaccta tcgagaaaac aatttccaag 1020

gcaaaaggac agcctagaga accacaggtg tacgtgtatc ctccatcaag ggatgagctg 1080

acaaagaacc aggtcagcct gacttgtctg gtgaaaggat tctatccctc tgacattgct 1140

gtggagtggg aaagtaatgg ccagcctgag aacaattaca agaccacacc ccctgtgctg 1200

gactcagatg gcagcttcgc gctggtgagc aagctgaccg tcgacaaatc ccggtggcag 1260

caggggaatg tgtttagttg ttcagtcatg cacgaggcac tgcacaacca ttacacccag 1320

aagtcactgt cactgtcacc aggg 1344

<210> SEQ ID NO 221
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 221

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Asp Tyr
20 25 30

Thr Met Asp Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asp Val Asn Pro Asn Ser Gly Gly Ser Ile Tyr Asn Gln Arg Phe
50 55 60

Lys Gly Arg Phe Thr Leu Ser Val Asp Arg Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asn Leu Gly Pro Ser Phe Tyr Phe Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> SEQ ID NO 222
<211> LENGTH: 357
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 222

gaagtgcagc tggtcgaatc tggaggagga ctggtgcagc caggagggtc cctgcgcctg 60

tcttgcgccg ctagtggctt cacttttacc gactacacca tggattgggt gcgacaggca 120

cctggaaagg gcctggagtg ggtcgccgat gtgaacccaa atagcggagg ctccatctac 180

-continued

aaccagcggt tcaagggccg gttcaccctg tcagtggacc ggagcaaaaa caccctgtat 240

ctgcagatga atagcctgcg agccgaagat actgctgtgt actattgcgc ccggaatctg 300

gggccctcct tctactttga ctattggggg cagggaactc tggtcaccgt gagctcc 357

<210> SEQ ID NO 223
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 223

Gly Phe Thr Phe Thr Asp Tyr Thr
1 5

<210> SEQ ID NO 224
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 224

ggcttcactt ttaccgacta cacc 24

<210> SEQ ID NO 225
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 225

Ala Arg Asn Leu Gly Pro Ser Phe Tyr Phe Asp Tyr
1 5 10

<210> SEQ ID NO 226
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 226

gcccggaatc tggggccctc cttctacttt gactat 36

<210> SEQ ID NO 227
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 227

Val Asn Pro Asn Ser Gly Gly Ser
1 5

<210> SEQ ID NO 228

-continued

<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 228

gtgaacccaa atagcggagg ctcc 24

<210> SEQ ID NO 229
<211> LENGTH: 98
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 229

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val

<210> SEQ ID NO 230
<211> LENGTH: 294
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 230

gcctccacca agggaccttc tgtgttccca ctggctccct ctagtaaatc cacatctggg 60

ggaactgcag ccctgggctg tctggtgaag gactacttcc cagagcccgt cacagtgtct 120

tggaacagtg gcgctctgac ttctggggtc cacacctttc ctgcagtgct gcagtcaagc 180

gggctgtaca gcctgtcctc tgtggtcacc gtgccaagtt caagcctggg aacacagact 240

tatatctgca acgtgaatca caagccatcc aatacaaaag tcgacaagaa agtg 294

<210> SEQ ID NO 231
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 231

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1 5 10 15

-continued

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
50 55 60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
100 105 110

<210> SEQ ID NO 232
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 232

gcaccagagc tgctgggagg accaagcgtg ttcctgtttc cacccaagcc taaagataca 60

ctgatgatta gtaggacccc agaagtcaca tgcgtggtcg tggacgtgag ccacgaggac 120

cccgaagtca agtttaactg gtacgtggac ggcgtcgagg tgcataatgc caagactaaa 180

cccagggagg aacagtacaa cagtacctat cgcgtcgtgt cagtcctgac agtgctgcat 240

caggattggc tgaacgggaa agagtataag tgcaaagtga gcaataaggc tctgcccgca 300

cctatcgaga aaacaatttc caaggcaaaa 330

<210> SEQ ID NO 233
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 233

Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr Pro Pro Ser Arg Asp
1 5 10 15

Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
20 25 30

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
35 40 45

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
50 55 60

Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
65 70 75 80

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
85 90 95

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
100 105

<210> SEQ ID NO 234

-continued

<211> LENGTH: 318
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 234

ggacagccta gagaaccaca ggtgtacgtg tatcctccat caagggatga gctgacaaag 60

aaccaggtca gcctgacttg tctggtgaaa ggattctatc cctctgacat tgctgtggag 120

tgggaaagta atggccagcc tgagaacaat tacaagacca cacccctgt gctggactca 180

gatggcagct tcgcgctggt gagcaagctg accgtcgaca aatcccggtg gcagcagggg 240

aatgtgttta gttgttcagt catgcacgag gcactgcaca accattacac ccagaagtca 300

ctgtcactgt caccaggg 318

<210> SEQ ID NO 235
<211> LENGTH: 450
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 235

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr
20 25 30

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225 230 235 240

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Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                245                 250                 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            260                 265                 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        275                 280                 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
    290                 295                 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305                 310                 315                 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                325                 330                 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            340                 345                 350

Val Tyr Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
        355                 360                 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385                 390                 395                 400

Leu Asp Ser Asp Gly Ser Phe Ala Leu Val Ser Lys Leu Thr Val Asp
                405                 410                 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            420                 425                 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        435                 440                 445

Gly Lys
    450


<210> SEQ ID NO 236
<211> LENGTH: 1350
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide

<400> SEQUENCE: 236

gaggtgcagc tggtggaaag cggaggagga ctggtgcagc caggaggatc tctgcgactg     60

agttgcgccg cttcaggatt caacatcaag gacacctaca ttcactgggt gcgacaggct    120

ccaggaaaag gactggagtg ggtggctcga atctatccca ctaatggata cacccggtat    180

gccgactccg tgaaggggag gtttactatt agcgccgata catccaaaaa cactgcttac    240

ctgcagatga acagcctgcg agccgaagat accgctgtgt actattgcag tcgatgggga    300

ggagacggat tctacgctat ggattattgg ggacagggga ccctggtgac agtgagctcc    360

gcctctacca agggccccag tgtgtttccc ctggctcctt ctagtaaatc cacctctgga    420

gggacagccg ctctgggatg tctggtgaag gactatttcc ccgagcctgt gaccgtgagt    480

tggaactcag gcgccctgac aagcggagtg cacacttttc ctgctgtgct gcagtcaagc    540

gggctgtact ccctgtcctc tgtggtgaca gtgccaagtt caagcctggg cacacagact    600

tatatctgca acgtgaatca taagccctca aatacaaaag tggacaagaa agtggagccc    660
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aagagctgtg ataagaccca cacctgccct ccctgtccag ctccagaact gctgggagga 720

cctagcgtgt tcctgtttcc ccctaagcca aaagacactc tgatgatttc caggactccc 780

gaggtgacct gcgtggtggt ggacgtgtct cacgaggacc ccgaagtgaa gttcaactgg 840

tacgtggatg gcgtggaagt gcataatgct aagacaaaac caagagagga acagtacaac 900

tccacttatc gcgtcgtgag cgtgctgacc gtgctgcacc aggactggct gaacgggaag 960

gagtataagt gcaaagtcag taataaggcc ctgcctgctc caatcgaaaa aaccatctct 1020

aaggccaaag gccagccaag ggagccccag gtgtacgtgt acccacccag cagagacgaa 1080

ctgaccaaga accaggtgtc cctgacatgt ctggtgaaag gcttctatcc tagtgatatt 1140

gctgtggagt gggaatcaaa tggacagcca gagaacaatt acaagaccac acctccagtg 1200

ctggacagcg atggcagctt cgccctggtg tccaagctga cagtggataa atctcgatgg 1260

cagcagggga acgtgtttag ttgttcagtg atgcatgaag ccctgcacaa tcattacact 1320

cagaagagcc tgtccctgtc tcccggcaaa 1350

<210> SEQ ID NO 237
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 237

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr
20 25 30

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 238
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 238

gaggtgcagc tggtggaaag cggaggagga ctggtgcagc caggaggatc tctgcgactg 60

agttgcgccg cttcaggatt caacatcaag gacacctaca ttcactgggt gcgacaggct 120

ccaggaaaag gactggagtg ggtggctcga atctatccca ctaatggata cacccggtat 180

-continued

gccgactccg tgaaggggag gtttactatt agcgccgata catccaaaaa cactgcttac 240

ctgcagatga acagcctgcg agccgaagat accgctgtgt actattgcag tcgatgggga 300

ggagacggat tctacgctat ggattattgg ggacagggga ccctggtgac agtgagctcc 360

<210> SEQ ID NO 239
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 239

Gly Phe Asn Ile Lys Asp Thr Tyr
1 5

<210> SEQ ID NO 240
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 240

ggattcaaca tcaaggacac ctac 24

<210> SEQ ID NO 241
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 241

Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr
1 5 10

<210> SEQ ID NO 242
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 242

agtcgatggg gaggagacgg attctacgct atggattat 39

<210> SEQ ID NO 243
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 243

Ile Tyr Pro Thr Asn Gly Tyr Thr
1 5

<210> SEQ ID NO 244

-continued

<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 244

atctatccca ctaatggata cacc 24

<210> SEQ ID NO 245
<211> LENGTH: 98
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 245

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val

<210> SEQ ID NO 246
<211> LENGTH: 294
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 246

gcctctacca agggccccag tgtgtttccc ctggctcctt ctagtaaatc cacctctgga 60

gggacagccg ctctgggatg tctggtgaag gactatttcc ccgagcctgt gaccgtgagt 120

tggaactcag gcgccctgac aagcggagtg cacacttttc ctgctgtgct gcagtcaagc 180

gggctgtact ccctgtcctc tgtggtgaca gtgccaagtt caagcctggg cacacagact 240

tatatctgca acgtgaatca taagccctca aatacaaaag tggacaagaa agtg 294

<210> SEQ ID NO 247
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 247

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1 5 10 15

-continued

```
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
            100                 105                 110


<210> SEQ ID NO 248
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide

<400> SEQUENCE: 248

gctccagaac tgctgggagg acctagcgtg ttcctgtttc cccctaagcc aaaagacact     60

ctgatgattt ccaggactcc cgaggtgacc tgcgtggtgg tggacgtgtc tcacgaggac    120

cccgaagtga agttcaactg gtacgtggat ggcgtggaag tgcataatgc taagacaaaa    180

ccaagagagg aacagtacaa ctccacttat cgcgtcgtga gcgtgctgac cgtgctgcac    240

caggactggc tgaacgggaa ggagtataag tgcaaagtca gtaataaggc cctgcctgct    300

ccaatcgaaa aaaccatctc taaggccaaa                                     330


<210> SEQ ID NO 249
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 249

Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr Pro Pro Ser Arg Asp
1               5                   10                  15

Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
            20                  25                  30

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
        35                  40                  45

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
    50                  55                  60

Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
65                  70                  75                  80

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
                85                  90                  95

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
            100                 105


<210> SEQ ID NO 250
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-continued

<211> LENGTH: 318
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 250

ggccagccaa gggagcccca ggtgtacgtg tacccaccca gcagagacga actgaccaag 60

aaccaggtgt ccctgacatg tctggtgaaa ggcttctatc ctagtgatat tgctgtggag 120

tgggaatcaa atggacagcc agagaacaat tacaagacca cacctccagt gctggacagc 180

gatggcagct tcgccctggt gtccaagctg acagtggata aatctcgatg gcagcagggg 240

aacgtgttta gttgttcagt gatgcatgaa gccctgcaca atcattacac tcagaagagc 300

ctgtccctgt ctcccggc 318

<210> SEQ ID NO 251
<211> LENGTH: 232
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 251

Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
1 5 10 15

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
20 25 30

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
35 40 45

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
50 55 60

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
65 70 75 80

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
85 90 95

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
100 105 110

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
115 120 125

Arg Glu Pro Gln Val Tyr Val Leu Pro Pro Ser Arg Asp Glu Leu Thr
130 135 140

Lys Asn Gln Val Ser Leu Leu Cys Leu Val Lys Gly Phe Tyr Pro Ser
145 150 155 160

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
165 170 175

Leu Thr Trp Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
180 185 190

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
195 200 205

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
210 215 220

Ser Leu Ser Leu Ser Pro Gly Lys
225 230

-continued

<210> SEQ ID NO 252
<211> LENGTH: 696
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 252

gaacctaaaa gcagcgacaa gacccacaca tgccccctt gtccagctcc agaactgctg 60

ggaggaccaa gcgtgttcct gtttccaccc aagcccaaag atacactgat gatcagccga 120

actcccgagg tcacctgcgt ggtcgtggac gtgtcccacg aggaccccga agtcaagttc 180

aactggtacg tggacggcgt cgaagtgcat aatgcaaaga ctaaaccacg ggaggaacag 240

tacaactcta catatagagt cgtgagtgtc ctgactgtgc tgcatcagga ttggctgaac 300

ggcaaagagt ataagtgcaa agtgtctaat aaggccctgc ctgctccaat cgagaaaact 360

attagtaagg caaaagggca gcccagggaa cctcaggtct acgtgctgcc tccaagtcgc 420

gacgagctga ccaagaacca ggtctcactg ctgtgtctgg tgaaaggatt ctatccttcc 480

gatattgccg tggagtggga atctaatggc cagccagaga acaattacct gacctggccc 540

cctgtgctgg acagcgatgg gtccttcttt ctgtattcaa agctgacagt ggacaaaagc 600

agatggcagc agggaaacgt ctttagctgt tccgtgatgc acgaagccct gcacaatcat 660

tacacccaga agtctctgag tctgtcacct ggcaaa 696

<210> SEQ ID NO 253
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 253

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
50 55 60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
100 105 110

<210> SEQ ID NO 254
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

-continued

<400> SEQUENCE: 254

gctccagaac tgctgggagg accaagcgtg ttcctgtttc cacccaagcc caaagataca 60

ctgatgatca gccgaactcc cgaggtcacc tgcgtggtcg tggacgtgtc ccacgaggac 120

cccgaagtca agttcaactg gtacgtggac ggcgtcgaag tgcataatgc aaagactaaa 180

ccacgggagg aacagtacaa ctctacatat agagtcgtga gtgtcctgac tgtgctgcat 240

caggattggc tgaacggcaa agagtataag tgcaaagtgt ctaataaggc cctgcctgct 300

ccaatcgaga aaactattag taaggcaaaa 330

<210> SEQ ID NO 255
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 255

Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Leu Pro Pro Ser Arg Asp
1 5 10 15

Glu Leu Thr Lys Asn Gln Val Ser Leu Leu Cys Leu Val Lys Gly Phe
20 25 30

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
35 40 45

Asn Asn Tyr Leu Thr Trp Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
50 55 60

Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
65 70 75 80

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
85 90 95

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
100 105

<210> SEQ ID NO 256
<211> LENGTH: 318
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 256

gggcagccca gggaacctca ggtctacgtg ctgcctccaa gtcgcgacga gctgaccaag 60

aaccaggtct cactgctgtg tctggtgaaa ggattctatc cttccgatat tgccgtggag 120

tgggaatcta atggccagcc agagaacaat tacctgacct ggccccctgt gctggacagc 180

gatgggtcct tctttctgta ttcaaagctg acagtggaca aaagcagatg gcagcaggga 240

aacgtcttta gctgttccgt gatgcacgaa gccctgcaca atcattacac ccagaagtct 300

ctgagtctgt cacctggc 318

<210> SEQ ID NO 257
<211> LENGTH: 475
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

-continued

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 257

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                  10                  15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Ile Gly
            20                  25                  30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Ile Tyr Pro Tyr
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Gly Gly Gly Gly Ser
            100                 105                 110

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu
        115                 120                 125

Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys
    130                 135                 140

Ala Ala Ser Gly Phe Thr Phe Thr Asp Tyr Thr Met Asp Trp Val Arg
145                 150                 155                 160

Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Asp Val Asn Pro Asn
                165                 170                 175

Ser Gly Gly Ser Ile Tyr Asn Gln Arg Phe Lys Gly Arg Phe Thr Leu
            180                 185                 190

Ser Val Asp Arg Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu
        195                 200                 205

Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Asn Leu Gly Pro
    210                 215                 220

Ser Phe Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
225                 230                 235                 240

Ser Ala Ala Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro
                245                 250                 255

Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
            260                 265                 270

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
        275                 280                 285

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
    290                 295                 300

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
305                 310                 315                 320

Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
                325                 330                 335

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
            340                 345                 350

Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
        355                 360                 365

Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr Pro Pro Ser Arg Asp
    370                 375                 380
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Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
385                 390                 395                 400

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
                405                 410                 415

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
            420                 425                 430

Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
        435                 440                 445

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
    450                 455                 460

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
465                 470                 475


<210> SEQ ID NO 258
<211> LENGTH: 1425
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide

<400> SEQUENCE: 258

gacattcaga tgacccagag ccctagctcc ctgagtgcct cagtcgggga cagggtgact     60

atcacctgca aggcttcaca ggatgtcagc attggcgtgg catggtacca gcagaagcca    120

gggaaagcac ccaagctgct gatctatagc gcctcctaca ggtatacagg cgtgccatcc    180

cgcttctctg gcagtgggtc aggaactgac tttacactga ctatttctag tctgcagccc    240

gaagatttcg ccacatacta ttgccagcag tactatatct acccttatac ttttggccag    300

gggaccaaag tggagattaa gggcggagga ggctccggag gaggagggtc tggaggagga    360

ggaagtgagg tccagctggt ggaatctgga ggaggactgg tgcagccagg agggtccctg    420

aggctgtctt gtgccgctag tggcttcacc tttacagact acacaatgga ttgggtgcgc    480

caggcaccag gaaagggact ggaatgggtc gctgatgtga accctaatag cggaggctcc    540

atctacaacc agcggttcaa aggacggttc accctgtcag tggaccggag caagaacacc    600

ctgtatctgc agatgaacag cctgagagcc gaggatactg ctgtgtacta ttgcgccagg    660

aatctgggcc caagcttcta ctttgactat tgggggcagg gaacactggt cactgtgtca    720

agcgcagccg aacccaaatc ctctgataag actcacacct gcccaccttg tccagctcca    780

gagctgctgg gaggacctag cgtgttcctg tttccaccca agccaaaaga cactctgatg    840

atttctagaa cccctgaagt gacatgtgtg gtcgtggacg tcagtcacga ggaccccgaa    900

gtcaaattca actggtacgt ggatggcgtc gaggtgcata atgccaagac caaaccccga    960

gaggaacagt acaactcaac ctatcgggtc gtgagcgtcc tgacagtgct gcatcaggac   1020

tggctgaacg gcaaggagta taagtgcaaa gtgagcaaca aggctctgcc tgcaccaatc   1080

gagaagacca tttccaaggc taaagggcag ccccgcgaac ctcaggtcta cgtgtatcct   1140

ccaagccgag atgagctgac aaaaaaccag gtctccctga cttgtctggt gaagggattt   1200

tacccaagtg acatcgcagt ggagtgggaa tcaaatggcc agcccgaaaa caattataag   1260

accacacccc ctgtgctgga ctctgatggg agtttcgcac tggtctccaa actgaccgtg   1320

gacaagtctc ggtggcagca gggaaacgtc tttagctgtt ccgtgatgca cgaggccctg   1380
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cacaatcatt acacacagaa atctctgagt ctgtcacctg gcaag 1425

<210> SEQ ID NO 259
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 259

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Ile Gly
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Ile Tyr Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 260
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 260

gacattcaga tgacccagag ccctagctcc ctgagtgcct cagtcgggga cagggtgact 60

atcacctgca aggcttcaca ggatgtcagc attggcgtgg catggtacca gcagaagcca 120

gggaaagcac ccaagctgct gatctatagc gcctcctaca ggtatacagg cgtgccatcc 180

cgcttctctg gcagtgggtc aggaactgac tttacactga ctatttctag tctgcagccc 240

gaagatttcg ccacatacta ttgccagcag tactatatct acccttatac ttttggccag 300

gggaccaaag tggagattaa g 321

<210> SEQ ID NO 261
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 261

Gln Asp Val Ser Ile Gly
1 5

<210> SEQ ID NO 262
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

-continued

<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 262

caggatgtca gcattggc 18

<210> SEQ ID NO 263
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 263

Gln Gln Tyr Tyr Ile Tyr Pro Tyr Thr
1 5

<210> SEQ ID NO 264
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 264

cagcagtact atatctaccc ttatact 27

<210> SEQ ID NO 265
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 265

Ser Ala Ser
1

<210> SEQ ID NO 266
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 266

agcgcctcc 9

<210> SEQ ID NO 267
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 267

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

-continued

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Asp Tyr
20 25 30

Thr Met Asp Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asp Val Asn Pro Asn Ser Gly Gly Ser Ile Tyr Asn Gln Arg Phe
50 55 60

Lys Gly Arg Phe Thr Leu Ser Val Asp Arg Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asn Leu Gly Pro Ser Phe Tyr Phe Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> SEQ ID NO 268
<211> LENGTH: 357
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 268

gaggtccagc tggtggaatc tggaggagga ctggtgcagc caggagggtc cctgaggctg 60

tcttgtgccg ctagtggctt cacctttaca gactacacaa tggattgggt gcgccaggca 120

ccaggaaagg gactggaatg ggtcgctgat gtgaacccta atagcggagg ctccatctac 180

aaccagcggt tcaaaggacg gttcaccctg tcagtggacc ggagcaagaa caccctgtat 240

ctgcagatga acagcctgag agccgaggat actgctgtgt actattgcgc caggaatctg 300

ggcccaagct tctactttga ctattggggg cagggaacac tggtcactgt gtcaagc 357

<210> SEQ ID NO 269
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 269

Gly Phe Thr Phe Thr Asp Tyr Thr
1 5

<210> SEQ ID NO 270
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 270

ggcttcacct ttacagacta caca 24

<210> SEQ ID NO 271
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

-continued

<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 271

Ala Arg Asn Leu Gly Pro Ser Phe Tyr Phe Asp Tyr
1 5 10

<210> SEQ ID NO 272
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 272

gccaggaatc tgggcccaag cttctacttt gactat 36

<210> SEQ ID NO 273
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 273

Val Asn Pro Asn Ser Gly Gly Ser
1 5

<210> SEQ ID NO 274
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 274

gtgaacccta atagcggagg ctcc 24

<210> SEQ ID NO 275
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 275

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
50 55 60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys

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                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
            100                 105                 110


<210> SEQ ID NO 276
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide

<400> SEQUENCE: 276

gctccagagc tgctgggagg acctagcgtg ttcctgtttc cacccaagcc aaaagacact     60

ctgatgattt ctagaacccc tgaagtgaca tgtgtggtcg tggacgtcag tcacgaggac    120

cccgaagtca aattcaactg gtacgtggat ggcgtcgagg tgcataatgc caagaccaaa    180

ccccgagagg aacagtacaa ctcaacctat cgggtcgtga gcgtcctgac agtgctgcat    240

caggactggc tgaacggcaa ggagtataag tgcaaagtga gcaacaaggc tctgcctgca    300

ccaatcgaga agaccatttc caaggctaaa                                     330


<210> SEQ ID NO 277
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 277

Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Tyr Pro Pro Ser Arg Asp
1               5                   10                  15

Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
            20                  25                  30

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
        35                  40                  45

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
    50                  55                  60

Ala Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
65                  70                  75                  80

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
                85                  90                  95

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
            100                 105


<210> SEQ ID NO 278
<211> LENGTH: 318
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide

<400> SEQUENCE: 278

gggcagcccc gcgaacctca ggtctacgtg tatcctccaa gccgagatga gctgacaaaa     60

aaccaggtct ccctgacttg tctggtgaag ggattttacc caagtgacat cgcagtggag    120

tgggaatcaa atggccagcc cgaaaacaat tataagacca cacccctgt gctggactct     180
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gatgggagtt tcgcactggt ctccaaactg accgtggaca agtctcggtg gcagcaggga 240

aacgtcttta gctgttccgt gatgcacgag gccctgcaca atcattacac acagaaatct 300

ctgagtctgt cacctggc 318

<210> SEQ ID NO 279
<211> LENGTH: 450
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 279

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr
20 25 30

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
290 295 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys

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305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Val Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
355 360 365

Leu Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly Lys
450

<210> SEQ ID NO 280
<211> LENGTH: 1350
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 280

gaggtgcagc tggtggaaag cggaggagga ctggtgcagc caggaggatc tctgcgactg 60

agttgcgccg cttcaggatt caacatcaag gacacctaca ttcactgggt gcgacaggct 120

ccaggaaaag gactggagtg ggtggctcga atctatccca ctaatggata cacccggtat 180

gccgactccg tgaaggggag gtttactatt agcgccgata catccaaaaa cactgcttac 240

ctgcagatga acagcctgcg agccgaagat accgctgtgt actattgcag tcgatgggga 300

ggagacggat tctacgctat ggattattgg ggacagggga ccctggtgac agtgagctcc 360

gcctctacca agggccccag tgtgtttccc ctggctcctt ctagtaaatc cacctctgga 420

gggacagccg ctctgggatg tctggtgaag gactatttcc ccgagcctgt gaccgtgagt 480

tggaactcag gcgccctgac aagcggagtg cacacttttc ctgctgtgct gcagtcaagc 540

gggctgtact ccctgtcctc tgtggtgaca gtgccaagtt caagcctggg cacacagact 600

tatatctgca acgtgaatca taagccctca aatacaaaag tggacaagaa agtggagccc 660

aagagctgtg ataagaccca cacctgccct ccctgtccag ctccagaact gctgggagga 720

cctagcgtgt tcctgtttcc ccctaagcca aaagacactc tgatgatttc caggactccc 780

gaggtgacct gcgtggtggt ggacgtgtct cacgaggacc ccgaagtgaa gttcaactgg 840

tacgtggatg gcgtggaagt gcataatgct aagacaaaac caagagagga acagtacaac 900

tccacttatc gcgtcgtgag cgtgctgacc gtgctgcacc aggactggct gaacgggaag 960

gagtataagt gcaaagtcag taataaggcc ctgcctgctc caatcgaaaa aaccatctct 1020

aaggccaaag gccagccaag ggagccccag gtgtacgtgc tgccacccag cagagacgaa 1080

-continued

ctgaccaaga accaggtgtc cctgctgtgt ctggtgaaag gcttctatcc tagtgatatt 1140

gctgtggagt gggaatcaaa tggacagcca gagaacaatt acctgacctg gcctccagtg 1200

ctggacagcg atggcagctt cttcctgtat tccaagctga cagtggataa atctcgatgg 1260

cagcagggga acgtgtttag ttgttcagtg atgcatgaag ccctgcacaa tcattacact 1320

cagaagagcc tgtccctgtc tcccggcaaa 1350

<210> SEQ ID NO 281
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 281

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr
20 25 30

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 282
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 282

gaggtgcagc tggtggaaag cggaggagga ctggtgcagc caggaggatc tctgcgactg 60

agttgcgccg cttcaggatt caacatcaag gacacctaca ttcactgggt gcgacaggct 120

ccaggaaaag gactggagtg ggtggctcga atctatccca ctaatggata cacccggtat 180

gccgactccg tgaaggggag gtttactatt agcgccgata catccaaaaa cactgcttac 240

ctgcagatga acagcctgcg agccgaagat accgctgtgt actattgcag tcgatgggga 300

ggagacggat tctacgctat ggattattgg ggacagggga ccctggtgac agtgagctcc 360

<210> SEQ ID NO 283
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

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<400> SEQUENCE: 283

Gly Phe Asn Ile Lys Asp Thr Tyr
1 5

<210> SEQ ID NO 284
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 284

ggattcaaca tcaaggacac ctac 24

<210> SEQ ID NO 285
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 285

Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr
1 5 10

<210> SEQ ID NO 286
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 286

agtcgatggg gaggagacgg attctacgct atggattat 39

<210> SEQ ID NO 287
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 287

Ile Tyr Pro Thr Asn Gly Tyr Thr
1 5

<210> SEQ ID NO 288
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 288

atctatccca ctaatggata cacc 24

<210> SEQ ID NO 289
<211> LENGTH: 98

-continued

<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 289

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val

<210> SEQ ID NO 290
<211> LENGTH: 294
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 290

gcctctacca agggccccag tgtgtttccc ctggctcctt ctagtaaatc cacctctgga 60

gggacagccg ctctgggatg tctggtgaag gactatttcc ccgagcctgt gaccgtgagt 120

tggaactcag gcgccctgac aagcggagtg cacacttttc ctgctgtgct gcagtcaagc 180

gggctgtact ccctgtcctc tgtggtgaca gtgccaagtt caagcctggg cacacagact 240

tatatctgca acgtgaatca taagccctca aatacaaaag tggacaagaa agtg 294

<210> SEQ ID NO 291
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 291

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
50 55 60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys

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                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
            100                 105                 110


<210> SEQ ID NO 292
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide

<400> SEQUENCE: 292

gctccagaac tgctgggagg acctagcgtg ttcctgtttc cccctaagcc aaaagacact     60

ctgatgattt ccaggactcc cgaggtgacc tgcgtggtgg tggacgtgtc tcacgaggac    120

cccgaagtga agttcaactg gtacgtggat ggcgtggaag tgcataatgc taagacaaaa    180

ccaagagagg aacagtacaa ctccacttat cgcgtcgtga gcgtgctgac cgtgctgcac    240

caggactggc tgaacgggaa ggagtataag tgcaaagtca gtaataaggc cctgcctgct    300

ccaatcgaaa aaaccatctc taaggccaaa                                     330


<210> SEQ ID NO 293
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 293

Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Leu Pro Pro Ser Arg Asp
1               5                   10                  15

Glu Leu Thr Lys Asn Gln Val Ser Leu Leu Cys Leu Val Lys Gly Phe
            20                  25                  30

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
        35                  40                  45

Asn Asn Tyr Leu Thr Trp Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
    50                  55                  60

Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
65                  70                  75                  80

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
                85                  90                  95

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
            100                 105


<210> SEQ ID NO 294
<211> LENGTH: 318
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide

<400> SEQUENCE: 294

ggccagccaa gggagcccca ggtgtacgtg ctgccaccca gcagagacga actgaccaag     60

aaccaggtgt ccctgctgtg tctggtgaaa ggcttctatc ctagtgatat tgctgtggag    120

tgggaatcaa atggacagcc agagaacaat tacctgacct ggcctccagt gctggacagc    180
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gatggcagct tcttcctgta ttccaagctg acagtggata aatctcgatg gcagcagggg 240

aacgtgttta gttgttcagt gatgcatgaa gccctgcaca atcattacac tcagaagagc 300

ctgtccctgt ctcccggc 318

<210> SEQ ID NO 295
<211> LENGTH: 480
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 295

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Asn Thr Ala
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Pro
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Gly Gly Ser Gly Gly
100 105 110

Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Glu
115 120 125

Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser
130 135 140

Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr Tyr
145 150 155 160

Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala
165 170 175

Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val Lys
180 185 190

Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr Leu
195 200 205

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ser
210 215 220

Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln Gly
225 230 235 240

Thr Leu Val Thr Val Ser Ser Ala Ala Glu Pro Lys Ser Ser Asp Lys
245 250 255

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
260 265 270

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
275 280 285

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
290 295 300

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn

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305                 310                 315                 320

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
                325                 330                 335

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
            340                 345                 350

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
        355                 360                 365

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Val
    370                 375                 380

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Leu
385                 390                 395                 400

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
                405                 410                 415

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Leu Thr Trp Pro Pro Val Leu
            420                 425                 430

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
        435                 440                 445

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
    450                 455                 460

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
465                 470                 475                 480


<210> SEQ ID NO 296
<211> LENGTH: 1440
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide

<400> SEQUENCE: 296

gacattcaga tgacacagag ccccagctcc ctgagtgctt cagtcggcga cagggtgact     60

atcacctgcc gcgcatccca ggatgtcaac accgctgtgg catggtacca gcagaagcct    120

ggaaaagccc caaagctgct gatctacagc gcttccttcc tgtattctgg cgtgccaagt    180

cggttttctg gaagtagatc aggcactgac ttcacactga ctatctctag tctgcagccc    240

gaagattttg ccacctacta ttgccagcag cactatacca cacccctac attcggacag    300

ggcactaaag tggagattaa gggcgggtca ggcggaggga gcggaggagg gtccggagga    360

gggtctggag gagggagtgg agaggtccag ctggtggaat ctggaggagg actggtgcag    420

cctggaggct cactgcgact gagctgtgcc gcttccggct ttaacatcaa agacacatac    480

attcattggg tcaggcaggc accagggaag ggactggaat gggtggcccg catctatccc    540

acaaatgggt acactcgata tgccgacagc gtgaaaggac ggtttaccat ttctgctgat    600

accagtaaga acacagcata cctgcagatg aacagcctgc gcgcagagga tacagccgtg    660

tactattgca gtcgatgggg gggagacggc ttctacgcca tggattattg gggccagggg    720

actctggtca ccgtgtcaag cgcagccgaa cctaaatcct ctgacaagac ccacacatgc    780

ccaccctgtc ctgctccaga gctgctggga ggaccatccg tgttcctgtt tcctccaaag    840

cctaaagata cactgatgat tagccgcact cccgaagtca cctgtgtggt cgtggacgtg    900

tcccacgagg accccgaagt caagttcaac tggtacgtgg acggcgtcga ggtgcataat    960

gccaagacta aaccaagaga ggaacagtac aattcaacct atagggtcgt gagcgtcctg   1020
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acagtgctgc atcaggattg gctgaacggc aaggagtata agtgcaaagt gtctaacaag 1080

gccctgcccg ctcctatcga gaagactatt agcaaggcaa aagggcagcc acgggaaccc 1140

caggtctacg tgctgccccc tagcagagac gagctgacca aaaaccaggt ctccctgctg 1200

tgtctggtga agggctttta tcctagtgat atcgctgtgg agtgggaatc aaatgggcag 1260

ccagaaaaca attacctgac atggccaccc gtgctggaca gcgatgggtc cttctttctg 1320

tattccaaac tgactgtgga caagtctaga tggcagcagg gaaacgtctt cagctgttcc 1380

gtgatgcacg aggccctgca caatcattac acccagaagt ctctgagtct gtcacccggc 1440

<210> SEQ ID NO 297
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 297

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Asn Thr Ala
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Pro
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 298
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 298

gacattcaga tgacacagag ccccagctcc ctgagtgctt cagtcggcga cagggtgact 60

atcacctgcc gcgcatccca ggatgtcaac accgctgtgg catggtacca gcagaagcct 120

ggaaaagccc caaagctgct gatctacagc gcttccttcc tgtattctgg cgtgccaagt 180

cggttttctg gaagtagatc aggcactgac ttcacactga ctatctctag tctgcagccc 240

gaagattttg ccacctacta ttgccagcag cactatacca cacccctac attcggacag 300

ggcactaaag tggagattaa g 321

<210> SEQ ID NO 299
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

-continued

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 299

Gln Asp Val Asn Thr Ala
1 5

<210> SEQ ID NO 300
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 300

caggatgtca acaccgct 18

<210> SEQ ID NO 301
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 301

Gln Gln His Tyr Thr Thr Pro Pro Thr
1 5

<210> SEQ ID NO 302
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 302

cagcagcact ataccacacc ccctaca 27

<210> SEQ ID NO 303
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 303

Ser Ala Ser
1

<210> SEQ ID NO 304
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 304

agcgcttcc 9

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<210> SEQ ID NO 305
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 305

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr
20 25 30

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 306
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 306

gaggtccagc tggtggaatc tggaggagga ctggtgcagc ctggaggctc actgcgactg 60

agctgtgccg cttccggctt taacatcaaa gacacataca ttcattgggt caggcaggca 120

ccagggaagg gactggaatg ggtggcccgc atctatccca caaatgggta cactcgatat 180

gccgacagcg tgaaaggacg gtttaccatt tctgctgata ccagtaagaa cacagcatac 240

ctgcagatga acagcctgcg cgcagaggat acagccgtgt actattgcag tcgatggggg 300

ggagacggct tctacgccat ggattattgg ggccagggga ctctggtcac cgtgtcaagc 360

<210> SEQ ID NO 307
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 307

Gly Phe Asn Ile Lys Asp Thr Tyr
1 5

<210> SEQ ID NO 308
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 308

ggctttaaca tcaaagacac atac 24

<210> SEQ ID NO 309
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 309

Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr
1 5 10

<210> SEQ ID NO 310
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 310

agtcgatggg ggggagacgg cttctacgcc atggattat 39

<210> SEQ ID NO 311
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 311

Ile Tyr Pro Thr Asn Gly Tyr Thr
1 5

<210> SEQ ID NO 312
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 312

atctatccca caaatgggta cact 24

<210> SEQ ID NO 313
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 313

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1 5 10 15

-continued

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
50 55 60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
100 105 110

<210> SEQ ID NO 314
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 314

gctccagagc tgctgggagg accatccgtg ttcctgtttc ctccaaagcc taaagataca 60

ctgatgatta gccgcactcc cgaagtcacc tgtgtggtcg tggacgtgtc ccacgaggac 120

cccgaagtca agttcaactg gtacgtggac ggcgtcgagg tgcataatgc caagactaaa 180

ccaagagagg aacagtacaa ttcaacctat agggtcgtga gcgtcctgac agtgctgcat 240

caggattggc tgaacggcaa ggagtataag tgcaaagtgt ctaacaaggc cctgcccgct 300

cctatcgaga agactattag caaggcaaaa 330

<210> SEQ ID NO 315
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 315

Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Leu Pro Pro Ser Arg Asp
1 5 10 15

Glu Leu Thr Lys Asn Gln Val Ser Leu Leu Cys Leu Val Lys Gly Phe
20 25 30

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
35 40 45

Asn Asn Tyr Leu Thr Trp Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
50 55 60

Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
65 70 75 80

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
85 90 95

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
100 105

<210> SEQ ID NO 316
<211> LENGTH: 318

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 316

gggcagccac gggaacccca ggtctacgtg ctgcccccta gcagagacga gctgaccaaa 60

aaccaggtct ccctgctgtg tctggtgaag ggcttttatc ctagtgatat cgctgtggag 120

tgggaatcaa atgggcagcc agaaaacaat tacctgacat ggccacccgt gctggacagc 180

gatgggtcct tctttctgta ttccaaactg actgtggaca agtctagatg gcagcaggga 240

aacgtcttca gctgttccgt gatgcacgag gccctgcaca atcattacac ccagaagtct 300

ctgagtctgt cacccggc 318

<210> SEQ ID NO 317
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 317

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Asn Thr Ala
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Pro
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> SEQ ID NO 318
<211> LENGTH: 642

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 318

gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggcaagtca ggacgttaac accgctgtag cttggtatca gcagaaacca 120

gggaaagccc ctaagctcct gatctattct gcatcctttt tgtacagtgg ggtcccatca 180

aggttcagtg gcagtcgatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240

gaagattttg caacttacta ctgtcaacag cattacacta ccccacccac tttcggccaa 300

gggaccaaag tggagatcaa acgaactgtg gctgcaccat ctgtcttcat cttcccgcca 360

tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat 420

cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccaa 480

gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg 540

ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc 600

ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt 642

<210> SEQ ID NO 319
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 319

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Asn Thr Ala
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Pro
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 320
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 320

gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggcaagtca ggacgttaac accgctgtag cttggtatca gcagaaacca 120

-continued

gggaaagccc ctaagctcct gatctattct gcatcctttt tgtacagtgg ggtcccatca 180

aggttcagtg gcagtcgatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240

gaagattttg caacttacta ctgtcaacag cattacacta ccccacccac tttcggccaa 300

gggaccaaag tggagatcaa a 321

<210> SEQ ID NO 321
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 321

Gln Asp Val Asn Thr Ala
1 5

<210> SEQ ID NO 322
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 322

caggacgtta acaccgct 18

<210> SEQ ID NO 323
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 323

Gln Gln His Tyr Thr Thr Pro Pro Thr
1 5

<210> SEQ ID NO 324
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 324

caacagcatt acactacccc acccact 27

<210> SEQ ID NO 325
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 325

Ser Ala Ser
1

-continued

<210> SEQ ID NO 326
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 326

tctgcatcc 9

<210> SEQ ID NO 327
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 327

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
1 5 10 15

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
20 25 30

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
35 40 45

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
50 55 60

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
65 70 75 80

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
85 90 95

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
100 105

<210> SEQ ID NO 328
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 328

cgaactgtgg ctgcaccatc tgtcttcatc ttcccgccat ctgatgagca gttgaaatct 60

ggaactgcct ctgttgtgtg cctgctgaat aacttctatc ccagagaggc caaagtacag 120

tggaaggtgg ataacgccct ccaatcgggt aactcccaag agagtgtcac agagcaggac 180

agcaaggaca gcacctacag cctcagcagc accctgacgc tgagcaaagc agactacgag 240

aaacacaaag tctacgcctg cgaagtcacc catcagggcc tgagctcgcc cgtcacaaag 300

agcttcaaca ggggagagtg t 321

<210> SEQ ID NO 329
<211> LENGTH: 231
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

-continued

polypeptide

<400> SEQUENCE: 329

Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
1 5 10 15

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
20 25 30

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
35 40 45

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
50 55 60

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
65 70 75 80

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
85 90 95

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
100 105 110

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
115 120 125

Arg Glu Pro Gln Val Tyr Val Leu Pro Pro Ser Arg Asp Glu Leu Thr
130 135 140

Lys Asn Gln Val Ser Leu Leu Cys Leu Val Lys Gly Phe Tyr Pro Ser
145 150 155 160

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
165 170 175

Leu Thr Trp Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
180 185 190

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
195 200 205

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
210 215 220

Ser Leu Ser Leu Ser Pro Gly
225 230

<210> SEQ ID NO 330
<211> LENGTH: 693
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polynucleotide

<400> SEQUENCE: 330

gaacctaaat ccagcgacaa gacccacaca tgccccctt gtccagctcc agaactgctg 60

ggaggaccaa gcgtgttcct gtttccaccc aagcccaaag atacactgat gatcagccga 120

actcccgagg tcacctgcgt ggtcgtggac gtgtcccacg aggaccccga agtcaagttc 180

aactggtacg tggacggcgt cgaagtgcat aatgcaaaga ctaaaccacg ggaggaacag 240

tacaactcta catatagagt cgtgagtgtc ctgactgtgc tgcatcagga ttggctgaac 300

ggcaaagagt ataagtgcaa agtgtctaat aaggccctgc ctgctccaat cgagaaaact 360

attagtaagg caaaagggca gcccagggaa cctcaggtct acgtgctgcc tccaagtcgc 420

gacgagctga ccaagaacca ggtctcactg ctgtgtctgg tgaaaggatt ctatccttcc 480

-continued

gatattgccg tggagtggga atctaatggc cagccagaga acaattacct gacctggccc 540

cctgtgctgg acagcgatgg gtccttcttt ctgtattcaa agctgacagt ggacaaaagc 600

agatggcagc agggaaacgt ctttagctgt tccgtgatgc acgaagccct gcacaatcat 660

tacacccaga agtctctgag tctgtcacct ggc 693

<210> SEQ ID NO 331
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 331

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
50 55 60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
100 105 110

<210> SEQ ID NO 332
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 332

gctccagaac tgctgggagg accaagcgtg ttcctgtttc cacccaagcc caaagataca 60

ctgatgatca gccgaactcc cgaggtcacc tgcgtggtcg tggacgtgtc ccacgaggac 120

cccgaagtca agttcaactg gtacgtggac ggcgtcgaag tgcataatgc aaagactaaa 180

ccacgggagg aacagtacaa ctctacatat agagtcgtga gtgtcctgac tgtgctgcat 240

caggattggc tgaacggcaa agagtataag tgcaaagtgt ctaataaggc cctgcctgct 300

ccaatcgaga aaactattag taaggcaaaa 330

<210> SEQ ID NO 333
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 333

Gly Gln Pro Arg Glu Pro Gln Val Tyr Val Leu Pro Pro Ser Arg Asp
1 5 10 15

-continued

Glu Leu Thr Lys Asn Gln Val Ser Leu Leu Cys Leu Val Lys Gly Phe
20 25 30

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
35 40 45

Asn Asn Tyr Leu Thr Trp Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
50 55 60

Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
65 70 75 80

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
85 90 95

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
100 105

<210> SEQ ID NO 334
<211> LENGTH: 318
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 334

gggcagccca gggaacctca ggtctacgtg ctgcctccaa gtcgcgacga gctgaccaag 60

aaccaggtct cactgctgtg tctggtgaaa ggattctatc cttccgatat tgccgtggag 120

tgggaatcta atggccagcc agagaacaat tacctgacct ggccccctgt gctggacagc 180

gatgggtcct tctttctgta ttcaaagctg acagtggaca aaagcagatg gcagcaggga 240

aacgtcttta gctgttccgt gatgcacgaa gccctgcaca atcattacac ccagaagtct 300

ctgagtctgt cacctggc 318

<210> SEQ ID NO 335
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 335

Val Asn Pro Asn Ser Gly Gly Ser
1 5

<210> SEQ ID NO 336
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 336

Ala Arg Asn Leu Gly Pro Ser Phe Tyr Phe Asp Tyr
1 5 10

<210> SEQ ID NO 337
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

-continued

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 337

Gly Phe Thr Phe Thr Asp Tyr Thr
1 5

<210> SEQ ID NO 338
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 338

Ser Ala Ser
1

<210> SEQ ID NO 339
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 339

Gln Gln Tyr Tyr Ile Tyr Pro Tyr Thr
1 5

<210> SEQ ID NO 340
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 340

Gln Asp Val Ser Ile Gly
1 5

<210> SEQ ID NO 341
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 341

Ile Tyr Pro Thr Asn Gly Tyr Thr
1 5

<210> SEQ ID NO 342
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 342

Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr

-continued

1 5 10

<210> SEQ ID NO 343
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 343

Gly Phe Asn Ile Lys Asp Thr Tyr
1 5

<210> SEQ ID NO 344
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 344

Ser Ala Ser
1

<210> SEQ ID NO 345
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 345

Gln Gln His Tyr Thr Thr Pro Pro Thr
1 5

<210> SEQ ID NO 346
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 346

Gln Asp Val Asn Thr Ala
1 5

<210> SEQ ID NO 347
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 347

Gln Gln Tyr Tyr Ile Tyr Pro Ala Thr
1 5

<210> SEQ ID NO 348
<211> LENGTH: 8
<212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 348

Gly Phe Thr Phe Ala Asp Tyr Thr
1 5

<210> SEQ ID NO 349
<211> LENGTH: 607
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 349

Thr Gln Val Cys Thr Gly Thr Asp Met Lys Leu Arg Leu Pro Ala Ser
1 5 10 15

Pro Glu Thr His Leu Asp Met Leu Arg His Leu Tyr Gln Gly Cys Gln
20 25 30

Val Val Gln Gly Asn Leu Glu Leu Thr Tyr Leu Pro Thr Asn Ala Ser
35 40 45

Leu Ser Phe Leu Gln Asp Ile Gln Glu Val Gln Gly Tyr Val Leu Ile
50 55 60

Ala His Asn Gln Val Arg Gln Val Pro Leu Gln Arg Leu Arg Ile Val
65 70 75 80

Arg Gly Thr Gln Leu Phe Glu Asp Asn Tyr Ala Leu Ala Val Leu Asp
85 90 95

Asn Gly Asp Pro Leu Asn Asn Thr Thr Pro Val Thr Gly Ala Ser Pro
100 105 110

Gly Gly Leu Arg Glu Leu Gln Leu Arg Ser Leu Thr Glu Ile Leu Lys
115 120 125

Gly Gly Val Leu Ile Gln Arg Asn Pro Gln Leu Cys Tyr Gln Asp Thr
130 135 140

Ile Leu Trp Lys Asp Ile Phe His Lys Asn Asn Gln Leu Ala Leu Thr
145 150 155 160

Leu Ile Asp Thr Asn Arg Ser Arg Ala Cys His Pro Cys Ser Pro Met
165 170 175

Cys Lys Gly Ser Arg Cys Trp Gly Glu Ser Ser Glu Asp Cys Gln Ser
180 185 190

Leu Thr Arg Thr Val Cys Ala Gly Gly Cys Ala Arg Cys Lys Gly Pro
195 200 205

Leu Pro Thr Asp Cys Cys His Glu Gln Cys Ala Ala Gly Cys Thr Gly
210 215 220

Pro Lys His Ser Asp Cys Leu Ala Cys Leu His Phe Asn His Ser Gly
225 230 235 240

Ile Cys Glu Leu His Cys Pro Ala Leu Val Thr Tyr Asn Thr Asp Thr
245 250 255

Phe Glu Ser Met Pro Asn Pro Glu Gly Arg Tyr Thr Phe Gly Ala Ser
260 265 270

Cys Val Thr Ala Cys Pro Tyr Asn Tyr Leu Ser Thr Asp Val Gly Ser
275 280 285

Cys Thr Leu Val Cys Pro Leu His Asn Gln Glu Val Thr Ala Glu Asp
290 295 300

Gly Thr Gln Arg Cys Glu Lys Cys Ser Lys Pro Cys Ala Arg Val Cys

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305                 310                 315                 320

Tyr Gly Leu Gly Met Glu His Leu Arg Glu Val Arg Ala Val Thr Ser
                325                 330                 335

Ala Asn Ile Gln Glu Phe Ala Gly Cys Lys Lys Ile Phe Gly Ser Leu
            340                 345                 350

Ala Phe Leu Pro Glu Ser Phe Asp Gly Asp Pro Ala Ser Asn Thr Ala
        355                 360                 365

Pro Leu Gln Pro Glu Gln Leu Gln Val Phe Glu Thr Leu Glu Glu Ile
    370                 375                 380

Thr Gly Tyr Leu Tyr Ile Ser Ala Trp Pro Asp Ser Leu Pro Asp Leu
385                 390                 395                 400

Ser Val Phe Gln Asn Leu Gln Val Ile Arg Gly Arg Ile Leu His Asn
                405                 410                 415

Gly Ala Tyr Ser Leu Thr Leu Gln Gly Leu Gly Ile Ser Trp Leu Gly
            420                 425                 430

Leu Arg Ser Leu Arg Glu Leu Gly Ser Gly Leu Ala Leu Ile His His
        435                 440                 445

Asn Thr His Leu Cys Phe Val His Thr Val Pro Trp Asp Gln Leu Phe
    450                 455                 460

Arg Asn Pro His Gln Ala Leu Leu His Thr Ala Asn Arg Pro Glu Asp
465                 470                 475                 480

Glu Cys Val Gly Glu Gly Leu Ala Cys His Gln Leu Cys Ala Arg Gly
                485                 490                 495

His Cys Trp Gly Pro Gly Pro Thr Gln Cys Val Asn Cys Ser Gln Phe
            500                 505                 510

Leu Arg Gly Gln Glu Cys Val Glu Glu Cys Arg Val Leu Gln Gly Leu
        515                 520                 525

Pro Arg Glu Tyr Val Asn Ala Arg His Cys Leu Pro Cys His Pro Glu
    530                 535                 540

Cys Gln Pro Gln Asn Gly Ser Val Thr Cys Phe Gly Pro Glu Ala Asp
545                 550                 555                 560

Gln Cys Val Ala Cys Ala His Tyr Lys Asp Pro Pro Phe Cys Val Ala
                565                 570                 575

Arg Cys Pro Ser Gly Val Lys Pro Asp Leu Ser Tyr Met Pro Ile Trp
            580                 585                 590

Lys Phe Pro Asp Glu Glu Gly Ala Cys Gln Pro Cys Pro Ile Asn
        595                 600                 605


<210> SEQ ID NO 350
<211> LENGTH: 217
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 350

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                   10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60
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Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly Lys
    210                 215
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We claim:

1. A method of treating a subject having a tumor; inhibiting, reducing or blocking HER2 signaling; or killing or inhibiting the growth of a HER2-expressing tumor cell, the method comprising administering an effective amount of an antigen binding construct comprising:

a first antigen-binding polypeptide construct which monovalently and specifically binds a HER2 (human epidermal growth factor receptor 2) ECD2 (extracellular domain 2) antigen on a HER2-expressing cell;

a second antigen-binding polypeptide construct which monovalently and specifically binds a HER2 ECD4 (extracellular domain 4) antigen on a HER2-expressing cell;

first and second linker polypeptides, wherein the first linker polypeptide is operably linked to the first antigen-binding polypeptide construct, and the second linker polypeptide is operably linked to the second antigen-binding polypeptide construct;

wherein the linker polypeptides are capable of forming a covalent linkage with each other,

wherein one or both of the first or the second antigen binding polypeptide construct is an scFv,

wherein the dissociation constant (K_D) of the antigen binding construct to murine HER2 extracellular domain as measured by surface plasmon resonance (SPR) is equal to or less than the dissociation constant of a monospecific anti-HER2 ECD4 antibody (v506; SEQ ID NO:1 and SEQ ID NO:317) to murine HER2 extracellular domain as measured by surface plasmon resonance (SPR), and

wherein tumor growth is decreased as compared to a control receiving an equivalent amount of a non-specific control antibody, as compared to a control receiving an equivalent amount of Herceptin/trastuzumab, or as compared to a control not receiving treatment.

2. The method of claim **1** wherein the antigen binding construct comprises the full length sequences set forth in SEQ ID NOs 97, 295, and 69 (v10000), and optionally wherein the dissociation constant (K_D) of the construct to murine HER2 extracellular domain as measured by surface plasmon resonance (SPR) is approximately 0.6 nM.

3. A method of treating a subject having a tumor; inhibiting, reducing or blocking HER2 signaling; or killing or inhibiting the growth of a HER2-expressing tumor cell, the method comprising administering an effective amount of an antigen binding construct comprising:

a first antigen-binding polypeptide construct which monovalently and specifically binds a HER2 (human epidermal growth factor receptor 2) ECD2 (extracellular domain 2) antigen on a HER2-expressing cell, wherein the first antigen-binding polypeptide construct comprises a first variable light-chain (VL1) domain and a first variable heavy-chain (VH1) domain, wherein the first antigen-binding polypeptide construct comprises VH1 and VL1 CDR sequences that are at least 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identical to the VH1 and VL1 CDR sequences of v7091 (SEQ ID NOs 223, 225, 227, 37, 39, and 41), and wherein the VL1 domain comprises 1, 2, 3, 4, or 5 amino acid substitutions and/or the VH1 domain comprises 1, 2, 3, 4, or 5 amino acid substitutions;

a second antigen-binding polypeptide construct which monovalently and specifically binds a HER2 ECD4 (extracellular domain 4) antigen on a HER2-expressing cell;

first and second linker polypeptides, wherein the first linker polypeptide is operably linked to the first antigen-binding polypeptide construct, and the second linker polypeptide is operably linked to the second antigen-binding polypeptide construct;

wherein one or both of the first or the second antigen binding polypeptide construct is an scFv,

wherein the linker polypeptides are capable of forming a covalent linkage with each other, and

wherein tumor growth is decreased as compared to a control receiving an equivalent amount of a non-specific control antibody, as compared to a control receiving an equivalent amount of Herceptin/trastuzumab, or as compared to a control not receiving treatment.

4. The method of any of the above claims, wherein the binding affinity of the antigen binding construct to murine HER2 extracellular domain as measured by surface plasmon resonance (SPR) is greater than the binding affinity of v7091 (SEQ ID NOs 33, 219, and 295) to murine HER2 extracellular domain as measured by surface plasmon resonance (SPR), optionally wherein the antigen binding construct and v7091 bind the same epitope, optionally wherein the antigen binding construct binds the same epitope as pertuzamab, optionally wherein the antigen binding construct has a greater Bmax than v7091, and optionally wherein the antigen binding construct is internalized to a greater extent upon cell surface binding relative to v7091.

5. The method of any of the above claims, wherein the binding affinity of the antigen binding construct to murine HER2 extracellular domain as measured by surface plasmon resonance (SPR) is equal to or greater than the binding affinity of a monospecific anti-HER2 ECD4 antibody (v506; SEQ ID NO:1 and SEQ ID NO:317) to murine HER2 extracellular domain as measured by surface plasmon resonance (SPR).

6. The method of any of the above claims, wherein the first antigen-binding polypeptide construct comprises the VH1 and VL1 CDR sequences of v7091 (SEQ ID NOs 223, 225, 227, 37, 39, and 41), wherein the VL1 domain comprises 1, 2, 3, 4, or 5 amino acid substitutions and/or the VH1 domain comprises 1, 2, 3, 4, or 5 amino acid substitutions, optionally wherein the first antigen-binding polypeptide construct comprises a substitution at Y96 in the VL1 domain (SEQ ID NO:35), optionally wherein the first antigen-binding polypeptide construct comprises a Y96A substitution in the VL1 domain (SEQ ID NO:35), optionally wherein the first antigen-binding polypeptide construct comprises substitutions at T30, A49, and/or L69 in the VH1 domain (SEQ ID NO:221), optionally wherein the first antigen-binding polypeptide construct comprises T30A, A49G, and/or L69F substitution(s) in the VH1 domain (SEQ ID NO:221), and optionally wherein the first antigen-binding polypeptide construct comprises T30A, A49G, and L69F substitution(s) in the VH1 domain (SEQ ID NO:221).

7. The method of any of the above claims, wherein the second antigen-binding polypeptide construct comprises VH2 and VL2 CDR sequences that are at least 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identical to the VH2 and VL2 CDR sequences of v10000 (SEQ ID NOs 299, 301, 303, 307, 309, and 311), optionally wherein the second antigen-binding polypeptide construct comprises the VH2 and VL2 CDR sequences of v10000 (SEQ ID NOs 299, 301, 303, 307, 309, and 311).

8. The method of any of the above claims, wherein the antigen binding construct comprises the variable domain sequences set forth in SEQ ID NOs 71 and/or 99, the variable domain sequences set forth in SEQ ID NOs 297 and/or 305, or the variable domain sequences set forth in SEQ ID NOs 71, 99, 297, and 305.

9. The method of any of the above claims, wherein the antigen binding construct comprises the full length sequence set forth in SEQ ID NO 97, the full length sequence set forth in SEQ ID NO 295, the full length sequence set forth in SEQ ID NO 69, or the full length sequences set forth in SEQ ID NOs 97, 295, and 69 (v10000).

10. The method of any of the above claims, wherein the first and second linker polypeptide each comprise an immunoglobulin hinge region polypeptide selected from an IgG1, IgG2 or IgG4 hinge region.

11. The method of any of the above claims, wherein the first and second linker polypeptides are operably linked to a scaffold, optionally an Fc.

12. The method of any of the above claims, wherein the first and second linker polypeptides are operably linked to a dimeric Fc comprising first and second Fc polypeptides each comprising a CH3 sequence, wherein the first Fc polypeptide is operably linked to the first linker polypeptide and the second Fc polypeptide is operably linked to the second linker polypeptide.

13. The method of any of the above claims, wherein (i) the first antigen binding polypeptide construct is an scFv and the second antigen binding polypeptide construct is a Fab; or (ii) the first antigen binding polypeptide construct is a Fab and the second antigen binding polypeptide construct is an scFv; or (iii) both the first antigen binding polypeptide construct and the second antigen binding polypeptide construct are scFvs.

14. The method of any of the above claims, wherein

i. the first antigen-binding polypeptide construct is a Fab and comprises

   a. a first heavy chain variable polypeptide VH1 comprising the VH of the pertuzumab arm of v5019, v 5020 v7091, v6717 or v10000 (SEQ ID NOs 221, 149, 221, 259, and 99, respectively), and

   b. a first variable light chain polypeptide VL1 comprising the VL of the pertuzumab arm of v5019, v 5020 v7091, v6717 or v10000 (SEQ ID NOs 35, 35, and 71 for v5019, v7091, and v10000, respectively); and

   the second antigen-binding polypeptide construct is an scFv and comprises

   (a) a second variable heavy chain polypeptide VH2 comprising the VH of the trastuzumab arm of v5019, v 5020 v7091, v6717 or v10000 (SEQ ID NOs 171, 205, 297, 171, and 297, respectively), and

   (b) a second variable light chain polypeptide VL2 comprising the VL of the trastzumab arm of v5019, v 5020 v7091, v6717 or v10000 (SEQ ID NO:35 for v5020); or

ii. the first antigen-binding polypeptide construct is an scFv and comprises

   (a) a first variable heavy chain polypeptide VH1 comprising the VH of the pertuzumab arm of v5019, v 5020 v7091, v6717 or v10000 (SEQ ID NOs 221, 149, 221, 259, and 99, respectively), and

   (b) a first variable light chain polypeptide VL1 comprising the VL of the pertuzumab arm of v5019, v 5020 v7091, v6717 or v10000 (SEQ ID NOs 35, 35, and 71 for v5019, v7091, and v10000, respectively), and

   the second antigen-binding polypeptide construct is an Fab and comprises

   (a) a second heavy chain variable polypeptide VH2 comprising the VH of the trastuzumab arm of v5019, v 5020 v7091, v6717 or v10000 (SEQ ID NOs 171, 205, 297, 171, and 297, respectively), and

(b) a second variable light chain polypeptide VL2 comprising the VL of the trastuzumab arm of v5019, v 5020 v7091, v6717 or v10000 (SEQ ID NO:35 for v5020); or

iii. the first antigen-binding polypeptide construct is an scFv and comprises

(a) a first heavy chain variable polypeptide VH1 comprising the VH of the pertuzumab arm of v5019, v 5020 v7091, v6717 or v10000 (SEQ ID NOs 221, 149, 221, 259, and 99, respectively), and

(b) a first variable light chain polypeptide VL1 comprising the VL of the pertuzumab arm of v5019, v 5020 v7091, v6717 or v10000 (SEQ ID NOs 35, 35, and 71 for v5019, v7091, and v10000, respectively), and

the second antigen-binding polypeptide construct is an scFv and comprises

(a) a second heavy chain variable polypeptide VH2 comprising the VH of the trastuzumab arm of v5019, v 5020 v7091, v6717 or v10000 (SEQ ID NOs 171, 205, 297, 171, and 297, respectively), and

(b) a second variable light chain polypeptide VL2 comprising the VL of the trastuzumab arm of v5019, v 5020 v7091, v6717 or v10000 (SEQ ID NO:35 for v5020).

15. The method of any of the above claims, wherein the first antigen-binding polypeptide construct is selected from:

i. a polypeptide construct comprising three VH CDR sequences comprising the amino acid sequences SEQ ID NO: 335, SEQ ID NO:336 and SEQ ID NO:337, or SEQ ID NO:335, SEQ ID NO:336, and SEQ ID NO:348;

ii. a polypeptide construct comprising three VH CDR sequences comprising amino acid sequences that are at least 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identical to the three VH CDR sequences of SEQ ID NO: 335, SEQ ID NO:336 and SEQ ID NO:337, or SEQ ID NO:335, SEQ ID NO:336, and SEQ ID NO:348;

iii. a polypeptide construct comprising three VL CDR sequences comprising the amino acid sequences of the three VL CDR sequences of SEQ ID NO: 338, SEQ ID NO:339 and SEQ ID NO:340, or SEQ ID NO:338, SEQ ID NO:347, and SEQ ID NO:340;

iv. a polypeptide construct comprising three VL CDR sequences that are at least 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identical to the amino acid sequences of the three VL CDR sequences are at least 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identical to SEQ ID NO: 338, SEQ ID NO:339 and SEQ ID NO:340, or SEQ ID NO:338, SEQ ID NO:347, and SEQ ID NO:340;

v. a polypeptide construct comprising six CDR sequences comprising the amino acid sequences of the six CDR sequences of SEQ ID NO: 335, SEQ ID NO:336, SEQ ID NO:337, SEQ ID NO: 338, SEQ ID NO:339 and SEQ ID NO:340; or SEQ ID NO:335, SEQ ID NO:336, SEQ ID NO:348, SEQ ID NO:338, SEQ ID NO:347, and SEQ ID NO:340; or

vi. a polypeptide construct comprising six CDR sequences comprising the amino acid sequences that are at least 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identical to the six CDR sequences of SEQ ID NO: 335, SEQ ID NO:336, SEQ ID NO:337, SEQ ID NO: 338, SEQ ID NO:339 and SEQ ID NO:340; or SEQ ID NO:335, SEQ ID NO:336, SEQ ID NO:348, SEQ ID NO:338, SEQ ID NO:347, and SEQ ID NO:340; and

the second antigen-binding polypeptide is selected from

vii. a polypeptide construct comprising three VH CDR sequences comprising the amino acid sequences of the three VH CDR sequences of SEQ ID NO: 341, SEQ ID NO:342 and SEQ ID NO:343;

viii. a polypeptide construct comprising three VH CDR sequences comprising amino acids sequences that are at least 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identical to the three VH CDR sequences of SEQ ID NO: 341, SEQ ID NO:342 and SEQ ID NO:343;

ix. a polypeptide construct comprising three VL CDR sequences comprising the amino acid sequences of the three VL CDR sequences of SEQ ID NO: 344, SEQ ID NO:345 and SEQ ID NO:346;

x. a polypeptide construct comprising three VL CDR sequences that are at least 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identical to the amino acid sequences of the three VL CDR sequences of SEQ ID NO: 344, SEQ ID NO:345 and SEQ ID NO:346;

xi. a polypeptide construct comprising six CDR sequences comprising the amino acid sequences of the six CDR sequences of SEQ ID NO: 341, SEQ ID NO:342, SEQ ID NO:343, SEQ ID NO: 344, SEQ ID NO:345 and SEQ ID NO:346; or

xii. a polypeptide construct comprising six CDR sequences comprising the amino acid sequences that are at least 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identical to the six CDR sequences of SEQ ID NO: 341, SEQ ID NO:342, SEQ ID NO:343, SEQ ID NO: 344, SEQ ID NO:345 and SEQ ID NO:346.

16. The method of any of the above claims wherein the first antigen binding polypeptide construct: (i) blocks by 50% or greater the binding of pertuzumab to ECD2, and/or (ii) the second antigen binding polypeptide blocks by 50% or greater the binding of trastuzumab to ECD4.

17. The method according to any preceding claim wherein the first antigen binding polypeptide construct comprises one of the v5019, v10000, v7091, v5020 or v6717 antigen binding polypeptide constructs specific for HER2 ECD2, and the second antigen binding polypeptide construct comprises one of the v5019, v10000, v7091, v5020 or v6717 antigen-binding polypeptide constructs specific for HER2 ECD4.

18. The method according to any preceding claim, wherein the first antigen-binding polypeptide construct comprises an amino acid sequence at least 80%, 90%, 95%, 96%, 97%, 98%, or 99% identical to the v5019, v10000, v7091, v5020 or v6717 antigen-binding polypeptide construct specific for HER2 ECD2 and the second antigen-binding polypeptide construct comprises an amino acid sequence at least 80%, 90%, 95%, 96%, 97%, 98%, or 99% identical to the v5019, v10000, v7091, v5020 or v6717 antigen-binding polypeptide construct specific for HER2 ECD4.

19. The method according to any preceding claim, selected from v5019, v10000, v7091, v5020 and v6717.

20. The method according to any preceding claim, wherein the first antigen binding polypeptide construct is an Fab and the second antigen binding polypeptide construct is an scFv, and wherein the antigen binding construct

(i) induces increased receptor internalization in HER2 3+ cells and/or

(ii) displays higher potency in an ADCC (antibody directed cellular cytotoxicity) assay against HER2 1+ cells, and/or

(iii) comprises one or more of the characteristics described in one or more of the Examples, Tables, and Figures,

as compared to a reference biparatopic antigen binding construct having two Fabs.

21. The method according to according to any preceding claim, wherein the first and second antigen binding polypeptide constructs are scFvs, and wherein the antigen binding construct induces increased receptor internalization in HER2 1+, 2+ and 3+ cells as compared to a reference antigen binding construct having two Fabs.

22. The method according to any preceding claim, wherein the antigen-binding construct comprises an Fc, optionally wherein the Fc is a heterodimeric Fc.

23. The method according to any preceding claim, wherein the antigen-binding construct comprises a heterodimeric Fc, wherein the dimerized CH3 sequences have a melting temperature (Tm) of about 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 77.5, 78, 79, 80, 81, 82, 83, 84, or 85° C. or higher.

24. The method according to any preceding claim, wherein the antigen-binding construct comprises a heterodimeric Fc formed with a purity greater than about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% when expressed.

25. The method according to any preceding claim, wherein the antigen-binding construct comprises a heterodimeric Fc formed with a purity greater than about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% when expressed via a single cell.

26. The method according to any preceding claim, wherein the antigen-binding construct comprises a heterodimeric Fc comprising one or more modifications in at least one of the CH3 sequences.

27. The method according to any preceding claim, wherein the antigen-binding construct comprises a heterodimeric Fc comprising one or more modifications in at least one of the CH3 sequences that promote the formation of a heterodimer with stability comparable to a wild-type homodimeric Fc.

28. The method according to any preceding claim, wherein the antigen-binding construct comprises:

i. a heterodimeric IgG1 Fc having the modifications L351Y_F405A_Y407V in the first Fc polypeptide, and the modifications T366L_K392M_T394W in the second polypeptide;

ii. a heterodimeric IgG1 Fc having the modifications L351Y_F405A_Y407V in the first Fc polypeptide, and the modifications T366L_K392L_T394W in the second Fc polypeptide;

iii. a heterodimeric IgG1 Fc having the modifications T350V_L351Y_F405A_Y407V in the first Fc polypeptide, and the modifications T350V_T366L_K392L_T394W in the second Fc polypeptide;

iv. a heterodimeric IgG1 Fc having the modifications T350V_L351Y_F405A_Y407V in the first Fc polypeptide, and the modifications T350V_T366L_K392M_T394W in the second Fc polypeptide;

v. a heterodimeric IgG1 Fc having the modifications T350V_L351Y_S400E_F405A_Y407V in the first Fc polypeptide, and the modifications T350V_T366L_N390R_K392M_T394W in the second Fc polypeptide,

vi. a heterodimeric IgG1 Fc having the modifications T350V_L351Y_F405A_Y407V in the first Fc polypeptide, and the modifications T366I_N390R_K392M_T394W in the second Fc polypeptide; or

vii. a heterodimeric IgG1 Fc having the modifications L351Y_S400E_F405A_Y405V in the first Fc polypeptide, and the modifications T350V_T366L_K392L_T394W in the second Fc polypeptide;

according to EU numbering compared to a wild-type homodimeric Fc.

29. The method according to any preceding claim, wherein the antigen-binding construct comprises a heterodimeric Fc comprising at least one CH2 domain.

30. The method according to claim **29**, wherein the CH2 domain(s) of the heterodimeric Fc comprises one or more modifications.

31. The method according to any preceding claim, wherein the antigen-binding construct comprises a heterodimeric Fc comprising one or more modifications to promote selective binding of Fc-gamma receptors.

32. The method according to any preceding claim, wherein the antigen-binding construct comprises at least one modification, and wherein the modification is afucosylation.

33. The method according to any preceding claim, wherein the antigen-binding construct is conjugated to a drug.

34. The method construct according to claim **33**, wherein the drug is maytansine (DM1).

35. The method according to claim **34**, wherein the construct is conjugated to DM1 through an SMCC linker.

36. The method according to any preceding claim, wherein the antigen-binding construct is formulated in a pharmaceutical composition with a pharmaceutical carrier.

37. The method claim **36**, wherein the pharmaceutical carrier comprises a buffer, an antioxidant, a low molecular weight molecule, a drug, a protein, an amino acid, a carbohydrate, a lipid, a chelating agent, a stabilizer, or an excipient.

38. The method according to any preceding claim, wherein the result of the treatment is shrinking the tumor, inhibiting growth of the tumor, increasing time to progression of the tumor, prolonging disease-free survival of the subject, decreasing metastases, increasing the progression-free survival of the subject, or increasing overall survival of the subject.

39. The method according to any preceding claim, wherein the tumor comprises cells that express an average of 10,000 or more copies of HER2 per tumor cell, optionally wherein the tumor is HER2 gene-amplified.

40. The method according to any preceding claim, wherein the tumor is HER2 1+, HER2 2+ or HER2 3+ as determined by immunohistochemistry (IHC).

41. The method according to any preceding claim, wherein the tumor expresses HER2 at a level of 2+ or lower as determined by IHC.

42. The method according to any preceding claim, wherein the HER2+ tumor is a breast cancer that expresses HER2 at a 2+ level or lower, as determined by immunohistochemistry (IHC).

43. The method according to any preceding claim, wherein the tumor is a lung tumor, optionally wherein the

tumor is a non-squamous non-small cell lung tumor that is HER2-low, non-HER2 gene amplified.

44. The method of claim **43**, wherein the tumor is HER3+.

45. The method of claim **43** or **44**, wherein the tumor is EGFR low.

46. The method of claim **43**, **44**, or **45**, wherein the tumor is moderately sensitive to Cisplatin at the MTD.

47. The method according to any preceding claim, wherein the tumor is a head and neck tumor, optionally wherein the tumor is a squamous cell tumor of the head and neck that is HER2 low, non-HER2 gene amplified.

48. The method of claim **47**, wherein the tumor is HER3+ low.

49. The method of claim **47** or **48**, wherein the tumor is EGFR+.

50. The method of claim **47**, **48**, or **49**, wherein the tumor is highly sensitive to Cisplatin at the MTD.

51. The method according to any preceding claim, wherein the tumor is a breast tumor, optionally wherein the tumor is a ER+/PR− breast cancer with a luminal B molecular classification.

52. The method according to any preceding claim, wherein the tumor is a pancreatic tumor, optionally wherein the pancreatic tumor is HER2 negative as determined by IHC.

53. The method according to any preceding claim, wherein the tumor is a gastric tumor, optionally wherein the gastric tumor is HER2 3+.

54. The method according to any preceding claim, wherein the subject has not previously been treated with an anti-HER2 antibody.

55. The method according to any preceding claim, wherein the tumor is resistant or refractory to pertuzumab, trastuzumab and/or TDM1.

56. The method according to any preceding claim, wherein the subject has previously been treated with pertuzumab, trastuzumab and/or TDM1.

57. The method of any one of claims **1-41**, wherein the tumor is (i) a HER2 3+ estrogen receptor negative (ER−), progesterone receptor negative (PR−), trastuzumab resistant, chemotherapy resistant invasive ductal breast cancer, (ii) a HER2 3+ ER−, PR−, trastuzumab resistant inflammatory breast cancer, (iii) a HER2 3+, ER−, PR−, invasive ductal carcinoma or (iv) a HER2 2+ HER2 gene amplified trastuzumab and pertuzumab resistant breast cancer.

58. The method any one of claims **1-41** wherein the tumor cell is a HER2 1+ or 2+ human pancreatic carcinoma cell, a HER2 3+ human lung carcinoma cell, a HER2 2+ human Caucasian bronchioaveolar carcinoma cell, a human pharyngeal carcinoma cell, a HER2 2+ human tongue squamous cell carcinoma cell, a HER2 2+ squamous cell carcinoma cell of the pharynx, a HER2 1+ or 2+ human colorectal carcinoma cell, a HER2 3+ human gastric carcinoma cell, a HER2 1+ human breast ductal ER+ (estrogen receptor-positive) carcinoma cell, a HER2 2+/3+ human ER+, HER2-amplified breast carcinoma cell, a HER2 0+/1+ human triple negative breast carcinoma cell, a HER2 2+ human endometrioid carcinoma cell, a HER2 1+ lung-metastatic malignant melanoma cell, a HER2 1+ human cervix carcinoma cell, Her2 1+ human renal cell carcinoma cell, or a HER2 1+ human ovary carcinoma cell.

59. The method of any one of claims **1-41** wherein the tumor cell is a HER2 1+ or 2+ or 3+ human pancreatic carcinoma cell, a HER2 2+ metastatic pancreatic carcinoma cell, a HER2 0+/1+, +3+ human lung carcinoma cell, a HER2 2+ human Caucasian bronchioaveolar carcinoma cell, a HER2 0+ anaplastic lung carcinoma, a human non-small cell lung carcinoma cell, a human pharyngeal carcinoma cell, a HER2 2+ human tongue squamous cell carcinoma cell, a HER2 2+ squamous cell carcinoma cell of the pharynx, a HER2 1+ or 2+ human colorectal carcinoma cell, a HER2 0+, 1+ or 3+ human gastric carcinoma cell, a HER2 1+ human breast ductal ER+ (estrogen receptor-positive) carcinoma cell, a HER2 2+/3+ human ER+, HER2-amplified breast carcinoma cell, a HER2 0+/1+ human triple negative breast carcinoma cell, a HER2 0+ human breast ductal carcinoma (Basal B, Mesenchymal-like triple negative) cell, a HER2 2+ER+ breast carcinoma, a HER2 0+ human metastatic breast carcinoma cell (ER−, HER2− amplified, luminal A, TN), a human uterus mesodermal tumor (mixed grade III) cell, a 2+ human endometrioid carcinoma cell, a HER2 1+ human skin epidermoid carcinoma cell, a HER2 1+ lung-metastatic malignant melanoma cell, a HER2 1+ malignant melanoma cell, a human cervix epidermoid carcinoma vcell, a HER2 1+ human urinary bladder carcinoma cell, a HER2 1+ human cervix carcinoma cell, Her2 1+ human renal cell carcinoma cell, or a HER2 1+, 2+ or 3+ human ovary carcinoma cell, and wherein the antigen-binding construct is conjugated to maytansine (DM1).

60. The method of any one of claims **1-41** wherein the tumor cell is selected from a HER2 2/3+, gene amplified ovarian cancer cell, a HER2 0+/1+ triple negative breast cancer cell; an ER+, HER2 1+ breast cancer cell; a trastuzumab resistant HER2 2+ breast cancer cell; an ER+, HER2+ breast cancer cell; or a HER2 3+ breast cancer cell.

61. The method according to any preceding claim, wherein the construct is selected from v5019, v10000, v7091, v5020 or v6717.

62. The method according to any preceding claim, wherein administering is done by injection or infusion, optionally wherein the administering is intravenous.

63. The method according to any preceding claim, further comprising administering to the subject an additional agent, optionally a chemotherapeutic agent.

64. The method of claim **63**, wherein the additional agent is one or more of bleomycin, carboplatin, cisplatin, nab-paclitaxel, docetaxel, doxorubicin, erlotinib, fluorouracil, gemcitabine, methotrexate, pemetrexed, topotecan, vinorelbine, capecitabine, navelbine, or paclitaxel.

65. The method of claim **63**, wherein

i. the tumor is non-small cell lung cancer, and the additional agent is one or more of cisplatin, carboplatin, paclitaxel, albumin-bound paclitaxel, nab-paclitaxel, docetaxel, gemcitabine, vinorelbine, irinotecan, etoposide, vinblastine, capecitabine, navelbine or pemetrexed; or

ii. the tumor is head and neck cancer, and the additional agent is one or more of paclitaxel, carboplatin, doxorubicin or cisplatin; or

iii. the tumor is a estrogen and/or progesterone positive breast cancer, and the additional agent is one or more of doxorubicin, epirubicin, paclitaxel, nab-paclitaxel, docetaxel, fluorouracil, cyclophosphamide, carboplatin, letrozole, mifepristone, capecitabine, gemcitabine, vinorelbine or tamoxifen; or

iv. the tumor is a pancreatic tumor and the additional agent is nab-paclitaxel, capecitabine, gemcitabine, navelbine or paclitaxel.

66. The method according to any preceding claim, wherein the subject is a human.

67. The method according to any preceding claim, wherein the method comprises inhibiting, reducing or blocking HER2 signaling.

68. The method according to any preceding claim, wherein the method comprises killing or inhibiting the growth of a HER2-expressing tumor cell.

69. The method according to any preceding claim, wherein the subject is administered at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 doses.

70. The method according to any preceding claim, wherein the amount of at least one of the plurality of doses is at least 0.3, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 mg/kg.

71. The method according to any preceding claim, wherein the amount of each of the plurality of doses is at least 0.3, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 mg/kg.

72. The method according to any preceding claim, wherein each dose is administered at least daily, weekly, or monthly.

73. The method according to any preceding claim, wherein each dose is administered at least every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 days.

74. The method according to any preceding claim, wherein treatment continues for at least 1, 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, or 31 days; at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 weeks; or at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 months.

75. The method according to any preceding claim, wherein the mean tumor volume in the subject after receiving at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 doses is less than the mean tumor volume of a control subject receiving an equivalent amount of trastuzumab.

76. The method according to any preceding claim, wherein overall survival of the subject is significantly increased as compared to a control subject receiving an equivalent amount of a non-specific control antibody or as compared to a control subject not receiving treatment; or wherein the growth of tumor is significantly decreased as compared to a control subject receiving an equivalent amount of a non-specific control antibody, as compared to a control subject receiving an equivalent amount of Herceptin, or as compared to a control subject not receiving treatment.

77. The method of claim **76**, wherein the significance is measured by a log rank test.

78. The method of claim **76**, wherein the p value is less than 0.5, 0.01, or 0.001.

79. The method according to any preceding claim, wherein overall survival of the subject is more significantly increased as compared to a control subject receiving an equivalent amount of trastuzumab.

80. The method of claim **79**, wherein the antigen-binding construct p value is less than 0.001 and wherein the trastuzumab p value is greater than 0.001.

81. The method according to any preceding claim, wherein the p value of the significance of the increase relative to the control subject receiving an equivalent amount of a non-specific control antibody is less than the p value of an increase in survival of a second control receiving an equivalent amount of trastuzumab as compared to the control subject receiving an equivalent amount of a non-specific control antibody.

82. The method of claim **81**, wherein the antigen-binding construct p value is less than 0.001 and wherein the trastuzumab p value is greater than 0.001.

83. The method according to any preceding claim, wherein overall survival of the subject after receiving a combination of the antigen-binding construct and an additional agent is significantly increased as compared to a control subject receiving an equivalent amount of trastuzumab alone.

84. The method according to any preceding claim, wherein overall survival of the subject is significantly increased as compared to a control subject receiving a lesser amount of trastuzumab.

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